the diene obtained by recrystallization was 26%. Characteristic infrared bands for bibenzyl (900 and 1150 cm^{-1}) were prominent in the latter mother liquors from the diene.

Acknowledgment. The authors wish to express their appreciation to the donors of the Petroleum Research Fund for the support of this research under PRF Grant 723-A. Certain final aspects of this study were conducted under the auspices of the Public Health Service Grant GM-13421 at the Catholic University of America.

Factors Governing the Reaction of the Benzyl Grignard Reagent. I. Reactions with Acetaldehyde, Chloral, and Trifluoroacetaldehyde

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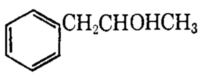
Abstract: The reaction of the benzyl Grignard reagent with acetaldehyde, chloral, and trifluoroacetaldehyde has been studied in detail. The products of the reaction with acetaldehyde are concentration dependent. With a 1:1 equivalency of Grignard to aldehyde, the principal product of the reaction is *o*-(2-hydroxypropyl)phenylmethylcarbinol. Benzylmethylcarbinol is a minor product and practically no *o*-tolylmethylcarbinol is produced. With a 3:1 equivalency of Grignard to aldehyde, all three products are formed. The intermediate leading to the diol product has been trapped out by adding trimethylchlorosilane to the reaction mixture at a time when hydrolysis would normally have been effected. The literature directions for the preparation of benzyltrichloromethylcarbinol from chloral could not be duplicated. Instead, halogen–metal exchange seemed to occur with the formation of bibenzyl and polymeric products. Also contrary to literature reports, it has been shown that benzyltrifluoromethylcarbinol is only a minor product when the benzyl Grignard reacts with trifluoroacetaldehyde. The products of this reaction are likewise dependent upon the relative concentrations of the Grignard and aldehyde. They are completely analogous to those obtained with acetaldehyde in that α, *ortho*, and diol products are formed.

The proclivity of the benzyl Grignard reagent to produce *ortho*- and *para*-substituted products in addition to the expected α has intrigued organic chemists through the years.[1] The so-called "abnormal reactions" of this reagent were first inadvertently noted by Grignard himself. In treating benzylmagnesium chloride with "polyoxymethylene," he characterized the product as the expected β-phenylethanol.[2] Tiffeneau and Delange[3] later disclosed that the material which Grignard had actually prepared was instead *o*-tolylcarbinol. Since this time, numerous examples have appeared in the chemical literature describing similar anomalies when the benzyl Grignard reacts with a variety of other reagents.

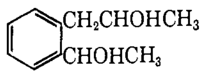
Unfortunately most of the early work in this field was hampered by the lack of adequate analytical techniques. The usual analytical method employed was oxidation of the crude reaction product to a mixture of benzoic, phthalic, and terephthalic acids. Such a method has two obvious flaws: (1) the yield of oxidation products is seldom quantitative and minor products can thus be overlooked; (2) one cannot safely extrapolate back to the structure of the materials which upon oxidation gave rise to the benzoic and phthalic acids.

Our laboratory is presently engaged in a broad, systematic research program designed to shed light, if possible, on those factors which influence benzylic-type Grignard reagents from reacting, on occasion, normally (*i.e.*, yield α products), and, under other circumstances, abnormally (*i.e.*, to form *ortho* and *para* products). In the present paper we are reporting the reaction of benzylmagnesium halides with acetaldehyde, chloral, and trifluoroacetaldehyde.

Acetaldehyde. Siegel[4] and co-workers, in an excellent series of papers, have studied the reaction between benzylmagnesium chloride and a variety of aldehydes. They report that the product of the reaction with acetaldehyde is a mixture of benzylmethylcarbinol (I) and *o*-(2-hydroxypropyl)phenylmethylcarbinol (II). They were unable to detect any *o*-tolylmethylcarbinol (III) in the reaction product. A similar pattern was noted for higher homologs like propionaldehyde, *n*-butyraldehyde, etc. It was pointed out that these results were in contrast to the reaction of the benzyl Grignard with formaldehyde in which only *o*-tolylcarbinol[5] is produced.



I



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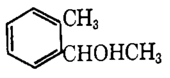

III

We repeated the reaction of the benzyl Grignard with acetaldehyde using a 1:1 and 3:1 equivalency of Grignard reagent to aldehyde, respectively. The products of

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(1) See H. Gilman and J. E. Kirby, *J. Am. Chem. Soc.*, 54, 345 (1932), for some pertinent literature references.

(2) M. V. Grignard, *Bull. Soc. Chim. France*, [3] 29, 953 (1903).

(3) M. Tiffeneau and R. Delange, *Compt. Rend.*, 137, 573 (1903).

(4) (a) S. Siegel, S. K. Coburn, and D. R. Levering, *J. Am. Chem. Soc.*, 73, 3163 (1951); (b) see also S. Siegel, W. M. Boyer, and R. R. Jay, *ibid.*, 73, 3237 (1951).

(5) As will be pointed out in the next paper in this series, this is an oversimplification in the case of formaldehyde.

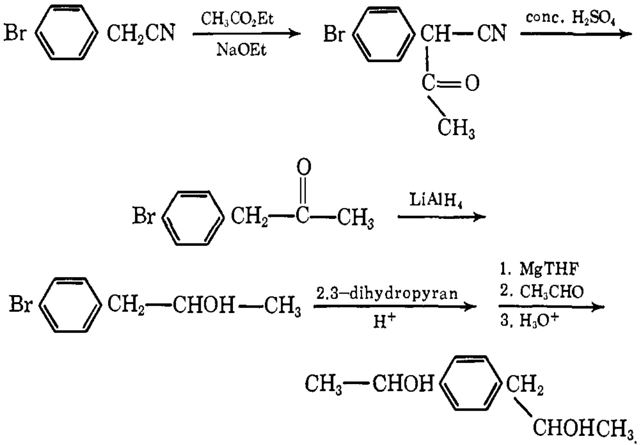
Table I. Reaction of Benzylmagnesium Chloride with Acetaldehyde[a]

Grignard: aldehyde ratio	Solvent	I, %	II, %	III, %
(1) 1:1	Et_2O	11[b]	76	<1
(2) 3:1	Et_2O	22	30	8
(3) 1:1	THF	43	32	1

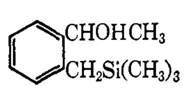
[a] The initial Grignard concentration was always 0.4 *N*. The aldehyde was dissolved in 50 ml of solvent and was added over a 40-min period. [b] In a duplicate run, there was 8% of I, 88% of II, and less than 1% of III obtained.

all reactions were analyzed by vapor phase chromatography (see Table I for results). With a 1:1 ratio of Grignard reagent to aldehyde, our results were quite comparable to those of Siegel[4] in that compounds I and II were the major products. Only a trace of *o*- and no *p*-tolylmethylcarbinol were formed under these conditions. Authentic samples of the two latter materials were at hand for comparison purposes. However, when the reaction was run with a 3:1 equivalency of Grignard reagent to aldehyde (*i.e.*, Grignard in excess) an 8% yield of *o*-tolylmethylcarbinol (III) was obtained in addition to compounds I and II. Hence, the reaction of acetaldehyde with the benzyl Grignard, like that with formaldehyde, is concentration dependent.[6] However, the tendency for this Grignard to form *o*-tolylcarbinol with formaldehyde is much greater than its tendency to form *o*-tolylmethylcarbinol with acetaldehyde.

It was also established with certainty that no *p*-(1-hydroxyethyl)benzylmethylcarbinol was produced in these reactions. An authentic sample of this compound for comparison purposes was prepared by the following sequence of reactions. The *para* isomer was a solid melting at 52° and was definitely *not* present in the reaction product. Hence, only α and *ortho* products were formed in the reaction with acetaldehyde.

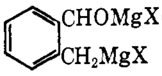


In still another experiment involving a 3:1 equivalency of Grignard to aldehyde, trimethylchlorosilane was added to the reaction when normally hydrolysis would have been carried out (after 1 hr of reaction time). There was no *o*-tolylmethylcarbinol detected among the reaction products in this experiment. Instead, *o*-(1-hydroxyethyl)benzyltrimethylsilane (IV) was isolated and identified by comparing it with an authentic sample. The latter was made by treating *o*-trimethylsilylmethylphenylmagnesium chloride with acetaldehyde.

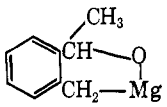


IV

The presence of IV clearly bespeaks for the intermediacy of a Grignard species akin to V or Va. Obviously, if such an intermediate is permitted to come into contact with acetaldehyde, it will react to form the diol II, a commonly observed product in these reactions. Also, since no *o*-tolylmethylcarbinol was formed in this experiment, one can conclude that the 8% of this material detected in an earlier experiment came about during the hydrolysis of the same intermediate responsible for the formation of IV.

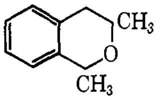


V

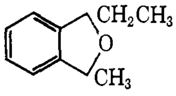


Va

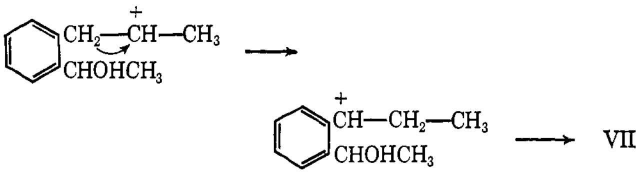
As confirmatory evidence that the high-boiling product obtained from the acetaldehyde reaction was structure II, it was dehydrated almost quantitatively with *p*-toluenesulfonic acid. This reaction produced cleanly only two products: 1,3-dimethylisochromane (VI) and 1-methyl-3-ethylisobenzofuran (VII). Compound VII probably arises through a 1,2-hydride shift during acid treatment.



VI



VII



Chloral. In order to assess the influence of electronic factors on the reaction between the benzyl Grignard and carbonyl compounds, the reaction with chloral was examined. This should be a highly reactive aldehyde toward attack by nucleophilic reagents and would be a convenient model to demonstrate the effect of electron-withdrawing substituents. Despite the fact that the claim had been made that this reaction yielded only "normal" product[7] (attack on α position), we failed completely in duplicating the published results. In our hands, this reaction consistently yielded rather large amounts of bibenzyl[8] in addition to high-boiling, polymeric residues. We were unable to obtain any products corresponding to the expected carbinols. We had at hand authentic samples of *o*- and *p*-tolyltrichloromethylcarbinols. These were stable compounds and amenable to column chromatography,

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(6) R. A. Benkeser, T. E. Johnston, J. M. Mallan, and A. E. Trevillyan, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p 1S.

(7) M. P. Hebert, *Bull Soc. Chim. France*, [4] 27, 45 (1920); J. W. Howard, *J. Am. Chem. Soc.*, **48**, 774 (1926); H. Gilman and R. K. Abbott, Jr., *J. Org. Chem.*, **8**, 224 (1943).

(8) It may be coincidental, but the boiling point of bibenzyl is rather close to that reported for benzyltrichloromethylcarbinol.[7]

distillation, and vapor phase chromatography. When the crude reaction product from the chloral reaction was subjected to these same purification techniques, no trace of the *ortho* and *para* products could be detected.

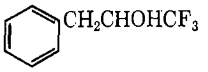
While we did not examine the reaction with chloral in great detail, our findings seem to parallel those of Reeve and Fine[9] who report that chloral, when treated with phenyllithium, undergoes no addition but rather that halogen–metal exchange occurs with the formation of chlorobenzene. If a similar reaction should occur with the benzyl Grignard, benzyl chloride would form. This would then couple with the unchanged Grignard reagent to form bibenzyl.

Trifluoroacetaldehyde. When chloral failed to give the expected reactions with the benzyl Grignard, we turned our attention to trifluoroacetaldehyde. In contrast to a literature report[10] which claimed that the α adduct was obtained exclusively in this reaction, we found it to be only a minor product. The pattern we observed for this reaction (see Table II) was very similar to that observed for acetaldehyde itself. In addition to the expected benzyltrifluoromethylcarbinol (VI), there was also obtained *o*-tolyltrifluoromethylcarbinol (VIII) and *o*-(2-hydroxy-3,3,3-trifluoropropyl)-phenyltrifluoromethylcarbinol (VII). The presence of compound VIII was confirmed by comparing it with an authentic sample. It could also be ascertained that *p*-tolyltrifluoromethylcarbinol was *not* present in the reaction mixture since an authentic sample of this isomer was also at hand for comparison purposes. Compound VI was identified by its elemental analysis, nmr spectrum (see Table III), and molecular weight. In addition, its vpc retention time was obviously different from the authentic *ortho* and *para* isomers. The diol (VII) was identified by its analysis, molecular weight, and nmr spectrum (Table III).

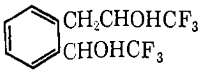
Table II. Reaction of Benzylmagnesium Chloride with Trifluoroacetaldehyde[a]

Grignard: aldehyde ratio	Solvent	VI, %	VII, %	VIII, %
(1) 1:1	Et_2O	1	92	<1
(2) 2:1[b]	Et_2O	13[c]	5	74
(3) 3:2[b]	Et_2O	16	38	36
(4) 1:1[b]	Et_2O	21[d]	70	8
(5) 1:1	THF	10	78	4

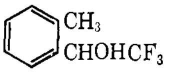
[a] The initial Grignard concentration was always 0.4 *N*. With liquid trifluoroacetaldehyde, the addition time was 40 min. The reaction time was 1 hr. [b] Gaseous aldehyde was used and was added in a stream of nitrogen. [c] A duplicate run here produced 12% of VI, 5% of VII, and 75% of VIII. [d] A duplicate run here produced 20% of VI, 70% of VII, and 8% of VIII.



VI



VII



VIII

There are several items of interest in Table II. When liquid trifluoroacetaldehyde was used rather than the gas, diol VII was the principal product. When gaseous aldehyde was employed and the Grignard/aldehyde ratio was gradually changed from 2:1 to 1:1 (entries 2, 3, and 4 in Table II), there was a gradual increase in diol product (VII) accompanied by a decrease in *o*-tolyltrifluoromethylcarbinol (VIII). The percentage of normal product (VI) always remained low. Hence this reaction, like that with acetaldehyde, is concentration dependent and analogous products are formed. As the concentration of aldehyde is increased relative to the Grignard reagent, the *o*-tolyltrifluoromethylcarbinol product diminishes in amount and the diol (VII) increases. With extremely high concentrations of aldehyde (as provided by the introduction of the liquid: entry 1, Table II), the diol is formed almost exclusively.

Conclusions. Our findings in connection with acetaldehyde offer support to the mechanism originally suggested by Johnson[11] and later modified by Young and Siegel[12] for the reaction of the benzyl Grignard with carbonyl compounds.

We have demonstrated for the first time that a concentration effect is operative in the reactions of the benzyl Grignard with acetaldehyde and trifluoroacetaldehyde as would be predicted by the proposed mechanism. We have also succeeded in "trapping out" the suggested intermediate (V or Va) in these reactions by causing it to react with trimethylchlorosilane to form *o*-(1-hydroxyethyl)benzyltrimethylsilane. Also of interest is the pronounced solvent effect brought about by tetrahydrofuran (entry 3, Table I). The amount of benzylmethylcarbinol is increased four- to fivefold when diethyl ether is replaced by this solvent. Since the composition of the Grignard reagent itself is often altered by a solvent[13] change, the situation is too complex to offer an explanation at this time.

$$\text{V or Va} \xrightarrow{(CH_3)_3SiCl} \text{IV}$$

The findings with regard to trifluoroacetaldehyde are worthy of comment. Both chloral and trifluoroacetaldehyde[14] have been reported to undergo facile reduction with Grignard reagents bearing β hydrogens. Normally the cyclic mechanism originally proposed by Whitmore[15] is employed to explain this reduction process. This mechanism involves initial complex formation between the carbonyl oxygen and the magnesium atom of the Grignard reagent. Previous workers[14] eliminated this mechanism from consideration when it was found that Henry's law constants were essentially unchanged by the addition of anhydrous magnesium bromide to a variety of fluorinated carbonyl compounds. It was concluded that both addition and reduction of fluorinated carbonyls probably proceeds by a direct attack of the Grignard reagent on the uncomplexed fluorine compound.[14] While this may very well be true, our observation that no *p*-tolyltrifluoromethylcarbinol was formed, but only *ortho* isomer, might be taken as some evidence for initial complex formation. Such a complex would nicely explain reaction at the *ortho* position to the exclusion of any *para* product. It would be necessary

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(9) W. Reeve and L. W. Fine, *J. Am. Chem. Soc.*, 86, 880 (1964).

(10) E. T. McBee, O. R. Pierce, and J. F. Higgins, *ibid.*, 74, 1736 (1952).

(11) J. R. Johnson, *ibid.*, 55, 3029 (1933).

(12) W. G. Young and S. Siegel, *ibid.*, 66, 354 (1944).

(13) E. C. Ashby and W. E. Becker, *ibid.*, 85, 119 (1963).

(14) E. T. McBee, O. R. Pierce, and D. D. Meyer, *ibid.*, 77, 83 (1955).

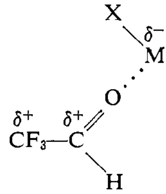
(15) F. C. Whitmore and R. S. George, *ibid.*, 64, 1239 (1942); see also, C. G. Swain and H. B. Boyles, *ibid.*, 73, 870 (1951); see also R. Hamelin, *Bull. Soc. Chim. France*, 926 (1961), for a modified version of this mechanism.

Table III. Nmr Spectra of Various Trifluoromethylcarbinols[a]

Alcohol	τ values
(1) o-CH$_3{}^1$C$_6$H$_4{}^2$CH^{3}OH^{4}CF$_3$	7.73 (H^1 singlet), 2.83 (H^2 multiplet), 4.90 (H^3 quartet), 6.61 (H^4 singlet)
(2) p-CH$_3{}^1$C$_6$H$_4{}^2$CH^{3}OH^{4}CF$_3$	7.69 (H^1 singlet), 2.87 (H^2 multiplet), 5.28 (H^3 quartet), 6.64 (H^4 singlet)
(3) C$_6$H$_5{}^1$CH$_2{}^2$CH^{3}OH^{4}CF$_3$	2.82 (H^1 multiplet), 7.26 (H^2, H^4 complex pattern), 6.18 (H^3 multiplet)
(4) o-CF$_3$CH^{1}OH^{2}C$_6$H$_4{}^3$CH$_2{}^4$CH^{5}OH^{6}CF$_3$	4.61 (H^1, H^6 complex pattern), 4.11 (H^2 doublet), 2.68 (H^3 multiplet), 6.98 (H^4 multiplet), 5.90 (H^5 multiplet)

[a] All spectra except for compound **4** were determined in carbon tetrachloride solution with tetramethylsilane as an internal standard. The spectra of **4** was determined in tetrahydrofuran-d_8 solution. A Varian A-60 nmr spectrometer was employed. Chemical shifts are measured from the estimated center of a singlet or multiplet. In the case of each spectra listed, the peak areas are quite consistent with the proton assignments made.

to assume the formation of only very small quantities of such a complex which would be very reactive to both addition and reduction because of the adjacent positive charges on the two carbon atoms of the aldehyde.[16]



Experimental Section

Preparation of Benzylmagnesium Chloride. To a 1-l., three-necked flask fitted with a mercury sealed stirrer, dropping funnel, and reflux condenser was added 24 g (1 g-atom) of magnesium turnings and sufficient anhydrous ether to cover the turnings. The entire system had been previously flushed with dry nitrogen, and all subsequent operations were carried out in a nitrogen atmosphere. A few milliliters of benzyl chloride was added to initiate the reaction and then sufficient anhydrous diethyl ether to give a total volume of about 500–600 ml. Then 63 g (0.5 mole) of pure benzyl chloride was added dropwise over a period of 4–6 hr. When addition was complete, the mixture was allowed to stir for an additional 1 to 5 hr.

The yields of benzylmagnesium chloride by this method were consistently in the range of 87–96% as determined by hydrolysis of an aliquot followed by titration with standard acid.

Benzylmagnesium Chloride and Acetaldehyde. All glassware was flamed out under dry nitrogen before use, and all subsequent reactions were carried out under nitrogen.

An appropriate amount of the Grignard solution was diluted with enough dry solvent to give 750 ml of a 0.4 *N* solution. The acetaldehyde, dissolved in 50 ml of dry solvent was added dropwise over a period of 40 min, and the mixture was allowed to stir for 1 hr.

Reaction mixtures were hydrolyzed with 20% aqueous ammonium chloride, and the ethereal solutions were dried over anhydrous magnesium sulfate followed by "Drierite." Solvent and any toluene formed during the reaction was removed under aspirator vacuum and the residue was vacuum distilled.

A mixture of benzylmethylcarbinol and *o*-tolylmethylcarbinol were distilled at 65–75° (0.75 mm). *o*-(2-Hydroxypropyl)phenylmethylcarbinol was distilled at 120–125° (0.2 mm). The distillation apparatus was washed with concentrated potassium hydroxide solution and distilled water before use. It was necessary to add about 0.5 g of potassium carbonate to the distillation flask to prevent the decomposition of the *o*-(2-hydroxypropyl)phenylmethylcarbinol.

The lower boiling fraction was analyzed by vpc on a 6-ft 5% FFAP on HMDS Ch W 60-80 stainless steel column at 150°; the high-boiling fraction was analyzed on the same column at 235°. An F & M Model 500 gas chromatograph was used equipped with a glass liner in the injection port.

The high-boiling fraction crystallized upon standing. One crystallization from ethyl acetate gave colorless crystals melting at 83–84° (lit.[4b] mp 83–84°).

Excess Benzylmagnesium Chloride and Acetaldehyde Followed by Addition of Trimethylchlorosilane. The reaction of acetaldehyde with a threefold excess of benzylmagnesium chloride was carried out in the usual manner, and the mixture was allowed to stir for 1 hr. Trimethylchlorosilane (2.0 moles) was added and the mixture was stirred for 24 hr and hydrolyzed with a 30% HCl solution. After drying, solvent was removed and the residue was vacuum distilled, the following fractions being taken: 40–50° (1 mm), 50–60° (0.5 mm), 60–62° (0.5 mm), 60–64° (0.2 mm), and 64–67° (0.2 mm). All fractions were analyzed using a 6-ft 20% FFAP on HMDS Ch W 60-80 stainless steel column at 175°. Benzylmethylcarbinol was present in all fractions but no *o*-tolylmethylcarbinol was observed. The last two fractions showed a peak in the gas chromatogram with the same retention time and infrared spectrum as an authentic sample of *o*-(1-hydroxyethyl)benzyltrimethylsilane.

When carbonation was attempted instead of the addition of trimethylchlorosilane, no *o*-(2-hydroxyethyl)phenyl acetic acid or the corresponding lactone could be detected. Analysis by vpc showed about 8% of *o*-tolylmethylcarbinol was present in the mixture.

Benzylmethylcarbinol. This compound was prepared by the LiAlH$_4$ reduction of benzyl methyl ketone. A product, boiling at 125° (25 mm) (lit.[17] bp 125° (25 mm)) was obtained.

***o*-Tolylmethylcarbinol.** The compound was prepared from *o*-tolylmagnesium bromide and acetaldehyde. A product, boiling at 108–109° (20 mm) (lit.[18] bp 107.8–108.0° (20 mm)) was obtained.

***p*-Tolylmethylcarbinol.** This compound was prepared from *p*-tolylmagnesium bromide and acetaldehyde. A product, boiling at 109–111° (19 mm) (lit.[18] bp 109–110° (19 mm)) was obtained.

1-(*p*-Bromophenyl)-1-cyano-2-propanone. This compound was prepared from 0.56 mole of *p*-bromobenzylnitrile, 0.88 mole of dry ethyl acetate, and 0.73 mole of sodium ethoxide in 193 ml of absolute ethanol. The mixture was heated on a steam bath for 2 hr and allowed to stand overnight. The mixture was cooled to 0° and filtered and the salt was washed with ether. The salt was dissolved in 375 ml of water, the solution was cooled to −10°, and 25 ml of glacial acetic acid was added with vigorous stirring. The product was filtered, a small portion recrystallized from methanol, and sublimed, mp 136–137°.

Anal. Calcd for C$_{10}$H$_8$BrNO: C, 50.42; H, 3.36; Br, 33.61. Found: C, 50.39; H, 3.60; Br, 33.82.

***p*-Bromobenzyl Methyl Ketone.** The crude, wet, crop of crystals obtained from the preparation of 1-(*p*-bromophenyl)-1-cyano-2-propanone was added to 88 ml of concentrated sulfuric acid at 0°. The mixture was heated on a steam bath until solution was complete, then for 5 min longer. It was cooled below 0°, 500 ml of water was added, and the mixture was heated on a steam bath for 2 hr with occasional shaking. The organic layer and ether extracts were dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was distilled giving 71 g (0.33 mole, 60%) of product boiling at 74° (0.15 mm). The distillate crystallized upon standing, mp 45–46°.

Anal. Calcd for C$_9$H$_9$BrO: C, 50.70; H, 4.23; Br, 37.56. Found: C, 50.73; H, 3.98; Br, 37.40.

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(16) It would be possible that the concentration of such a complex would be so small as to escape detection by vapor pressure determination or infrared: see H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *J. Am. Chem. Soc.*, **78**, 4374 (1956), and G. E. Dunn and J. Warkentin, *Can. J. Chem.*, 34, 75 (1956).

(17) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1124 (1914).

(18) F. Eisenlohr and L. Schulz, *Ber.*, 57, 1816 (1924).

1-(*p*-Bromophenyl)-2-propanol. To 7.6 g (0.2 mole) of $LiAlH_4$ in 200 ml of ether was added a solution of 42.6 g (0.200 mole) of *p*-bromobenzyl methyl ketone in 50 ml of dry ether. After stirring for 2 hr, 200 ml of a 20% aqueous ammonium chloride solution was added dropwise. The organic layer and ether extracts were dried over "Drierite"; the solvent was removed, and the residue was distilled. There was obtained 41.3 g (0.192 mole, 96%) of product boiling at 74–76° (0.2 mm), n^{20}D 1.5586.

Anal. Calcd for $C_9H_{11}BrO$: C, 50.23; H, 5.11; Br, 37.21. Found: C, 50.46; H, 4.90; Br, 37.40.

***p*-(1-Bromophenyl)-2-(2-tetrahydropyranyloxy)propane.** A mixture of 41.3 g (0.192 mole) of 1-(*p*-bromophenyl)-2-propanol, 84 g (1.0 mole) of 2,3-dihydropyran, and 5 drops of concentrated HCl was stirred for 2 days. The mixture was washed three times with a saturated $NaHCO_3$ solution dried over anhydrous K_2CO_3, and the excess dihydropyran was removed under aspirator vacuum. Distillation of the residue afforded 33 g (0.11 mole, 58%) of product boiling at 109–112° (0.17 mm), n^{18}D 1.5300.

Anal. Calcd for $C_{14}H_{19}BrO_2$: C, 56.20; H, 6.40; Br, 26.71. Found: C, 56.34; H, 6.60; Br, 26.90.

***p*-(1-Hydroxyethyl)benzylmethylcarbinol.** A mixture of 25 ml of dry tetrahydrofuran and 2.4 g (0.10 g-atom) of "activated" magnesium[19] was heated to 50°. A solution of 21 g (0.071 mole) of 1-(*p*-bromophenyl)-2-(2-tetrahydropyranyloxy)propane, in 25 ml of dry THF was added dropwise. The heat source was removed when vigorous refluxing started. After stirring for 2 hr, 3.5 g (0.08 mole) of acetaldehyde was added and the mixture was stirred for an additional hour. Hydrolysis was carried out with 100 ml of a 20% aqueous NH_4Cl solution. The organic layer and ether extracts were dried over "Drierite." Solvent was removed and the residue was dissolved in 100 ml of absolute ethanol. Five drops of concentrated hydrochloric acid were added; the mixture was stirred for 2 hr and poured into 400 ml of water. The organic layer and ether extracts were dried over "Drierite" and the solvent was removed. The resultant oil, totaling about 3 g, was purified by fractional sublimation. After about half the oil had been sublimed, crude crystals formed on the cold finger. These were removed, a seed crystal was replaced on the cold finger, and the remainder of the oil was sublimed, which also formed crystals. The solid was collected, recrystallized from an ethyl acetate–pentane solution, and resublimed, mp 52–52.5°.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.88. Found: C, 73.51; H, 8.99.

***o*-Chlorobenzyltrimethylsilane.** This compound was prepared from the Grignard reagent of *o*-chlorobenzyl chloride and trimethylchlorosilane. The product boiled at 110–112° (25 mm), n^{20}D 1.5122 (lit.[20] bp 222–223°, n^{20}D 1.5128).

***o*-(1-Hydroxyethyl)benzyltrimethylsilane (IV).** The Grignard reagent of *o*-chlorobenzyltrimethylsilane was prepared in refluxing tetrahydrofuran from 8.4 g (0.35 g-atom) of "activated" magnesium powder[14] and 69.5 g (0.35 mole) of the chloride, and the mixture was stirred for 8 hr. Acetaldehyde (17.6 g, 0.4 mole) was added, and the mixture was stirred for 1 hr and hydrolyzed with a 30% HCl solution. The organic layer and ether extracts were dried over anhydrous $MgSO_4$, then "Drierite," and the solvent was removed. Distillation of the residue afforded 53 g (0.22 mole, 63%) of product, bp 79–81° (0.35 mm), n^{20}D 1.5173.

Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.16; H, 9.67. Found: C, 69.46; H, 9.76.

Dehydration of *o*-(2-Hydroxypropyl)phenylmethylcarbinol. A mixture of 5.0 g (0.028 mole) of crude, crystalline *o*-(2-hydroxypropyl)phenylmethylcarbinol, 50 ml of glacial acetic acid, and 5 g of *p*-toluenesulfonic acid was heated on a steam bath for 1 hr. The acid solution was poured into 100 ml of a 20% potassium hydroxide solution, and the mixture was extracted with 100 ml of ether. The ethereal solution was washed exhaustively with a saturated sodium carbonate solution, then with water, and dried over "Drierite." Removal of the solvent afforded 4.4 g of an oil which was comprised of only two components as demonstrated by vpc analysis (15-ft DEGS at 150°). Structural assignments are based on analysis, infrared, nmr, and mass spectra.

The first peak (34%) was that of 1,3-dimethylisochromane. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 80.87; H, 8.60.

The second peak (66%) was that of 1-methyl-3-ethyl isobenzofuran. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.54; H, 9.02.

Total yield of products was 0.027 mole (98%). The reaction was repeated giving 4.3 g (96%) of the same mixture.

Benzylmagnesium Chloride and Chloral. This reaction was carried out in the same manner as the reaction with acetaldehyde, using 0.3 mole of chloral in 50 ml of ether and 0.3 equiv of a 0.4 *N* Grignard solution. Reactions were carried out at room temperature, at reflux, and at −20°. Hydrolyses were accomplished using 5% aqueous acetic acid and 20% aqueous ammonium chloride. A variety of work-up procedures was attempted, among them vacuum distillation at 18 mm and at 0.1 mm, sublimation, molecular distillation, vpc, and column chromatography. Aside from a black, tarry resin, only bibenzyl was recovered in 5–10% yield. More bibenzyl was recovered than could be accounted for from the preparation of the Grignard reagent.

Trifluoroacetaldehyde Hydrate. This compound was prepared according to the procedure of Pierce and Kane.[21] The product boiled at 102–108° (lit.[22] bp 103–105°).

Trifluoroacetaldehyde. This compound was prepared by the dehydration of trifluoroacetaldehyde hydrate.[23] The hydrate was added dropwise to a mixture of 81 ml of concentrated H_2SO_4 and 25 g of P_2O_5 heated to 80–85°. The free aldehyde, a gas at room temperature, was swept into a tared cold trap at −78° by means of a stream of dry N_2. Yields of 70–80% could be realized.

***o*-Tolyltrifluoromethylcarbinol.** This compound was prepared from *o*-tolylmagnesium bromide and trifluoroacetaldehyde. The product boiled at 104–106° (13 mm); n^{14}D 1.4730 (lit.[24] bp 108–109° (13 mm), n^{14}D 1.4728).

***p*-Tolyltrifluoromethylcarbinol.** This compound was prepared from *p*-tolylmagnesium bromide and trifluoroacetaldehyde. The product boiled at 91–94° (12 mm), n^{24}D 1.4644 (lit.[25] bp 94.5° (12 mm), n^{24}D 1.4650).

Benzylmagnesium Chloride and Trifluoroacetaldehyde. Trifluoroacetaldehyde (a gas at room temperature) was swept into a flask containing an appropriate amount of 0.4 *N* Grignard reagent by means of a stream of dry N_2. The aldehyde was contained in a trap at −10°. When the addition was complete, the reaction mixture was stirred for 1 hr, and worked up in the usual manner.

When liquid trifluoroacetaldehyde was used, a weighed amount of the aldehyde (contained in a cold trap at −78°) was transferred to a dry addition funnel. It was necessary to surround the funnel with a jacket of powdered Dry Ice in order to prevent the aldehyde from boiling. Fifty milliliters of cold, dry solvent was added to the aldehyde, and the reaction was carried out in the usual manner.

Benzyltrifluoromethylcarbinol and *o*-tolyltrifluoromethylcarbinol could be distilled at 82–85° (5 mm); however, this procedure usually caused partial decomposition of *o*-(2-hydroxy-3,3,3-trifluoropropyl)phenyltrifluoromethylcarbinol. The latter was crystallized from a petroleum ether (bp 35–37°)–diethyl ether mixture and was sublimed. It melted at 143–144°.

Anal. Calcd for $C_{11}H_{10}F_6O_2$: C, 45.83; H, 3.50; F, 39.57; mol wt, 288. Found: C, 46.13; H, 3.64; F, 39.80; mol wt, 291.

The benzyltrifluoromethylcarbinol and *o*-tolyltrifluoromethylcarbinol were separable by vpc (16-ft 5% FFAP on HMDS Ch W 60-80 stainless steel column) at any temperature between 175 and 250°. The *o*-tolyltrifluoromethylcarbinol was identified by comparing its retention time and infrared spectrum with that of an authentic sample.

The benzyltrifluoromethylcarbinol (n^{20}D 1.4589) was identified by its elemental analysis, infrared, and nmr spectra.

Anal. Calcd for $C_9H_9F_3O$: C, 56.83; H, 4.77; F, 29.99; mol wt, 190.2. Found: C, 56.49; H, 4.97; F, 30.35; mol wt, 204.

The ratio of benzyltrifluoromethylcarbinol to *o*-(2-hydroxy-3,3,3-trifluoropropyl)phenyltrifluoromethylcarbinol was obtained by vpc using a 16-ft 5% FFAP on HMDS Ch W 60-80 stainless steel column at 235°. Unfortunately this column would not separate an authentic mixture of *o*- and *p*-tolyltrifluoromethylcarbinols. The latter mixture could be separated on a 250-ft DEGS capillary column

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at 140°. As little as 0.1% of the *para* compound could be detected in the presence of the *ortho*.

Complete analysis was accomplished by using the packed column to obtain the ratio of benzyltrifluoromethylcarbinol to *o*-(2-hydroxy-3,3,3-trifluoropropyl)phenyltrifluoromethylcarbinol. The peak corresponding to the *o*-tolyltrifluoromethylcarbinol (possibly admixed with the *para* isomer) was collected and analyzed on the capillary column. No trace of the *para* isomer was detected.

Acknowledgment. This research was supported by the U. S. Army Research Office (Durham) to whom the authors are deeply indebted.

Some Aspects of Mechanism and Catalysis for Carbonyl Addition Reactions[1]

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Abstract: Benzaldehyde phenylhydrazone formation, like oxime, semicarbazone, and benzylideneaniline formation, occurs with rate-determining nucleophilic reagent attack under acidic conditions and with rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions. The Brønsted α value for general acid catalysis of the attack of phenylhydrazine on benzaldehyde is 0.20. The addition of urea to acetaldehyde exhibits both acid- and base-catalyzed reactions. This reaction too is subject to general acid catalysis which, in this case, is characterized by a Brønsted α value of 0.45. These values of α, together with several previously determined, are linearly related to the values of pK_a for the conjugate acids of the nucleophilic reagents. First-order rate constants for the hydrolysis, in slightly basic solution, of a series of benzylideneanilines substituted in the aniline moiety decrease slightly with increasing electron-withdrawing capacity of the polar substituent. The reaction of methoxyamine with a similar series of substituted benzylideneanilines is dependent on acid catalysis. Third-order rate constants for these reactions also decrease slightly with increasing electron-withdrawing capacity of the polar substituent.

This article reports the results of three lines of investigation relevant to mechanism and catalysis for carbonyl addition reactions. These studies include (i) examination of the variation in susceptibility to general acid catalysis as a function of the basicity of the attacking nucleophilic reagent, (ii) kinetic investigation of structure–reactivity correlations for the hydrolysis of a series of benzylideneanilines substituted in the aniline moiety, and (iii) elucidation of structure–reactivity correlations for the methoxyaminolysis of the same series of benzylideneanilines.

Previous studies have revealed that the attack of relatively weak nucleophilic reagents such as water,[3–8] thiourea,[9–11] semicarbazide,[12,13] aniline,[14] and phenylhydrazine[15] on carbonyl compounds is subject to general acid catalysis. In contrast, corresponding reactions involving stronger nucleophilic reagents such as hydroxylamine,[16] cyanide,[17] *t*-butylamine,[18] and sulfite[19,20] exhibit little or no catalysis of this type.[21] Consideration of multiple structure–reactivity correlations for general acid catalysis of carbonyl addition reactions reveals that the Brønsted α values, which are measures of susceptibility to catalysis of this type, should be linearly related to the pK_a of the conjugate acid of the nucleophilic reagent.[13,21] In an effort to examine more closely the validity of this conclusion and, in so doing, to gain further understanding of the variation in susceptibility to general acid–base catalysis as a function of reactivity, Brønsted α values for the attack of phenylhydrazine and urea on suitable carbonyl compounds have been determined.

Several studies of substituent effects on rates of Schiff base hydrolysis reveal that such effects may be reasonably complex. Early work is difficult to interpret since the nature of the rate-determining step at the values of pH employed is uncertain.[22,23] It is now clear that the pH–rate profiles for Schiff base hydrolysis are quite complex and that the observed structure–reactivity correlations are a sensitive function of the pH at which the reactions are studied.[14,18,24,25] Considerable attention has been devoted to the nature of the pH-independent reaction which is commonly observed

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[1] Supported by a grant from the National Institutes of Health (AM-08232).

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