be located with sufficient accuracy to exclude these possibilities.

1. Pedersen, C. Th. *Acta Chem. Scand.* 22 (1968) 247.
2. Eland, J. H. D. and Danby, C. J. *J. Chem. Soc.* **1965** 5935.
3. Meyerson, S., Drews, H. and Fields, E. K. *J. Am. Chem. Soc.* 86 (1964) 4964.
4. Johnstone, R. A. W. and Millard, B. J. *Z. Naturforsch.* 21a (1966) 604.
5. *Catalog of Mass Spectral Data*, American Petroleum Institute, Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., Spectrum No. 957.

Fig. 1. Relative concentrations (in per cent of 0.050 M) of reaction products at the time indicated in the reaction at 20° of 0.050 M methyl propionate with 0.50 M butylmagnesium bromide in ether solution. Methyl propionate □, dibutylethylcarbinol ○, 3-heptanone ×, 3-heptanol ●. Also shown is the relative concentration of dibutylethylcarbinol (in per cent of 0.005 M) for the reaction at 20° of 0.0050 M methyl propionate with 0.50 M butylmagnesium bromide △.

Mechanism of the Grignard Addition Reaction

VI. Product Distribution and Kinetics of the Reaction of Methyl Propionate with Butylmagnesium Bromide in Diethyl Ether

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In an earlier study [1] the kinetics of the reaction of methyl acetate with butylmagnesium bromide was investigated by means of a thermographic method. It seemed of interest, however, to follow this type of reaction by more conventional analytical methods. Gaschromatography of cause is the method of choice for determination of low boiling material in ether, but it was found convenient to use methyl propionate as the substrate instead of the acetate.

Quenching of the excess Grignard reagent which must precede the analytical process was found to be a difficult step, and rigorous precautions were necessary to avoid uncontrolled reaction during the work-up procedure. Whereas the thermographic method will handle very fast Grignard reactions (half lives of a few msec) methods
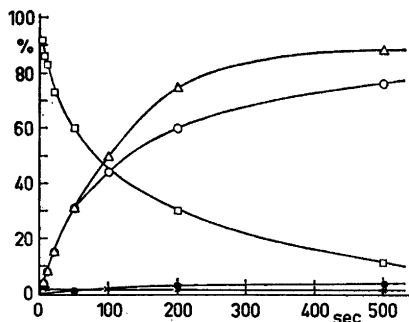
requiring quenching must be considered at least a thousand times slower.

Gaschromatographic analyses of the products from the reaction of 0.050 M methyl propionate with 0.500 M butylmagnesium bromide showed the presence of 3-heptanone, 3-heptanol, and dibutylethylcarbinol. Table 1 and Fig. 1 show the concentrations obtained at various times after mixing.

During the reaction the concentrations of ester and tertiary alcohol decrease, respectively increase in a complementary manner showing that no important build up of intermediates is taking place. The heptanol concentration increases in pace with the tertiary alcohol and accounts for approximately 5.5 % of the starting material at infinite reaction. The 3-heptanone concentration varies very little during the course of the reaction and accounts for 1.6 % of the starting material.

The reaction of 3-heptanone with butylmagnesium bromide was found to lead to very nearly the same concentrations of these three products. It therefore seems reasonable to assume that this ketone occurs as an actual intermediate and undergoes enolization, reduction, and addition in the ratios 1.6:5.5:90.

By means of the thermographic method [2] the initial rate of reaction of 3-heptanone

Table 1. Relative concentrations (in per cent of 0.050 M) of reaction products at the time indicated in the reaction at 20° of 0.050 M methyl propionate with 0.50 M butylmagnesium bromide in diethyl ether. k_1 is the apparent value of the first order rate constant for the formation of dibutyl-ethylcarbinol.

Time sec	$C_2H_5COOCH_3$	$(C_4H_9)_2C_2H_5COH$	$C_2H_5COC_4H_9$	$C_2H_5CHOHC_4H_9$	k_1 sec^{-1}
2	92	1.7	1.44	0.3	0.0083
5	86	4.0	1.68	0.4	0.0082
10	83	7.9	1.60	0.5	0.0083
20	73	15.3	1.52	0.6	0.0083
50	60	31	1.44	1.0	0.0074
100	45	44	1.60	2.2	0.0058
200	30.5	60	1.48	3.2	0.0046
500	11.4	77	1.60	4.0	0.0029
1000	2.9	85	1.64	4.8	
2000	0.0	90	1.88	5.5	

with butylmagnesium bromide in the concentrations used was found to be 64 times faster than the value found for methyl propionate. If the conversion of ester to tertiary alcohol consists of two consecutive steps (the free ketone being the intermediate) of which the second step is much faster than the first, an approximation of the kinetic equations would predict a ratio between the concentrations of ester and ketone very close to the inverse ratio of the rate constants for the two reactions, in the actual case 1:64 = 1.6 %.

In this way the concentrations of ketone found during the reaction may consist of two contributions: One part being the free ketone and amounting to 1.6 % of *unreacted* ester at the observation time and one part trapped as the enolate by enolization of the ketone during the reaction, and amounting to approximately 1.8 % of *consumed* ester. The sum of these two contributions is almost constant and the observation of the nearly invariant ketone concentration may thus be explained.

In the experiments a molar ratio of 10:1 of Grignard reagent to ester was used and in analogy with the results obtained with methyl acetate [2] the initial reaction is assumed to be first order with respect to ester. From Fig. 1 it is seen, however, that the ester is consumed relatively much more slowly at the end of the reaction than initially. Calculation of first order rate constants for the initial reaction (less than 20 % consumed ester) leads to the value 0.0083 sec^{-1} (Table 1) corresponding to a half life of 84 sec. The half life of the ester in the last part of the reaction is increased to 5−6 times this value.

Table 2. Relative concentrations (in per cent of 0.0050 M) of reaction product at the time indicated in the reaction at 20° of 0.0050 M methyl propionate with 0.50 M butylmagnesium bromide in diethyl ether. k_1 is the apparent value of the first order rate constant for the formation of dibutylethylcarbinol.

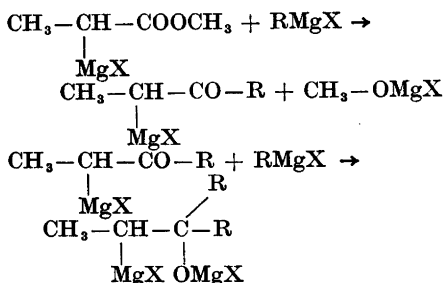| Time sec	$(C_4H_9)_2C_2H_5COH$	k_1
10	8.1	0.0084
20	14.9	0.0081
50	30.2	0.0072
100	50	0.0066
200	75	0.0070
500	89	
1000	93	
2000	89	

This deceleration of the reaction was much less conspicuous when the substrate was diluted 10 times (to 0.005 M) in which case an almost regular first order scheme was followed in the formation of tertiary alcohol as seen from Fig. 1 and Table 2.

It was furthermore observed that an extra amount of ester, when added to the reaction mixture after completion of the reaction, was consumed initially at the same rate as the first portion added (14 % tertiary alcohol formed in 20 sec).

These results seem to indicate that by reaction with a contaminated Grignard reagent (containing magnesium alcoholate etc.) the ester may be partly converted to a less reactive species from which ordinary ester is regenerated by the quenching process. This species is presumably the α-halomagnesium compound formed by the reaction:

$$CH_3CH_2COOCH_3 + RMgX \rightarrow$$

$$CH_3-CH-COOCH_3 + RH$$
$$\qquad\quad |$$
$$\qquad\quad MgX$$
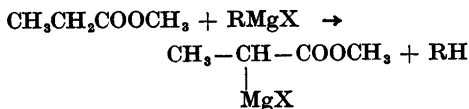
This type of compound is known to be formed from *tert*-butyl acetate and isopropylmagnesium chloride [3] and also by the conjugate addition of Grignard reagent to *sec*-butyl crotonate.[4,5] The α-halomagnesium esters react as Grignard reagents [3,5] but as they have usually been prepared carrying bulky ester alkyls they have not been known to show reactivity as Grignard substrates. Prepared from a straight chain methyl ester they may, however, be assumed to react as follows:

$$CH_3-CH-COOCH_3 + RMgX \rightarrow$$
$$\qquad |$$
$$\qquad MgX$$
$$CH_3-CH-CO-R + CH_3-OMgX$$
$$\qquad |$$
$$\qquad MgX$$
$$CH_3-CH-CO-R + RMgX \rightarrow$$
$$\qquad |\qquad\qquad R$$
$$\qquad MgX\qquad /$$
$$CH_3-CH-C-R$$
$$\qquad |\quad\;\; |$$
$$\qquad MgX\; OMgX$$

Products of this type were obtained by Fuson [6] in the addition of a Grignard reagent to an α,β-unsaturated ketone.

The problem of the existence of an α-halomagnesium ketone which in contrast to the isomeric ketone magnesium enolate is susceptible to attack by a Grignard reagent is being studied further.

Experimental. Dow triple sublimed magnesium was used. The reagents were prepared with rigorous exclusion of air, using an atmosphere of argon dried with phosphorus pentoxide and ether distilled from lithium-aluminium hydride. Dilutions were performed by the use of special measuring flasks in the form of all glass siphons which were sealed by polyethylene tubing. Dilution of the Grignard reagent to 10^{-4} M in this equipment did not cause turbidity of the solution. One stock solution (*ca.* 2 M) of butylmagnesium bromide was used for all runs and the bromine titration of this reagent exceeded the base titration by 3.1 %. The stock solution was diluted to 1.000 M (base titration) by the use of Metrohm piston burettes.

Methyl propionate was washed free of trace acid, dried with phosphorus pentoxide and distilled. A 0.100 M solution in dry ether was prepared and as internal standards were added 0.3 % heptane and 0.4 % dodecane.

For kinetic runs above 10 sec, 1 ml of Grignard reagent was mixed in a thermostated (20°) all glass syringe with 1 ml of the substrate solution. Reaction periods of 10 sec and less were obtained by the flowing stream technique described earlier.[6]

Quenching was performed by violent expression of the reaction mixture into 2 ml of 10 % methanol in ether cooled in a test tube in dry ice-acetone and immediately adding with stirring 0.5 ml of 6 M hydrochloric acid. The ether layer was treated with 2 ml of water and afterwards with 2 ml of 0.1 M sodium hydroxide followed by drying with magnesium sulphate.

The Aerograph 1520 gaschromatograph was used fitted with a flame ionization detector and a combination column consisting of 2 m sections of a polar (poly(ethylene glycol succinate) and a non-polar (silicone elastomer E 301) type filling. The peak-height corresponding to the various reaction products were corrected according to the peaks of the internal standards and taken as an indication of the relative concentration. Absolute concentrations were calculated by the analysis of standard solutions of the various products prepared with inclusion of the internal standards.

Rate constants were calculated on the basis of the concentrations of the tertiary alcohol only since the work up procedure apparently caused a loss of 5—8 % of the methyl propionate present.

The measurement of the rate constant for the reaction of 3-heptanone was performed in the flowing stream reactor as described [6] using a concentration of ketone and butylmagnesium bromide of, respectively, 0.05 M and 0.50 M (the Grignard reagent containing 3.1 % excess bromine by titration). A value of 0.53 sec^{-1} for the rate constant at 20° was obtained.

1. Holm, T. *Acta Chem. Scand.* **20** (1966) 2821.
2. Holm, T. *Acta Chem. Scand.* **21** (1967) 2753.
3. Dubois, J. E., Hennequin, F. and Durand, M. *Bull. Soc. Chim. France* **1963** 791.
4. Munch-Petersen, J. *Acta Chem. Scand.* **12** (1958) 967.
5. Holm, T. *Acta Chem. Scand.* **19** (1965) 1819.
6. Fuson, R. C., San, T. and Diekmann, J. *J. Org. Chem.* **27** (1962) 1221.