and lower peptide esters by repeated extraction with boiling water. A second crop of highly polymerized material (B) was prepared from the cold water-soluble peptide esters of the first experiment (on the average hexapeptides) by heating these in the dry state to 135° for three weeks.

The extent of polymerization was gauged by amino nitrogen determinations, rather than by alkoxyl analysis.[27] Fraction A representing 12 and 28%, respectively, of the theoretical yield, was composed of an average of 15 and 16 glycine units; fraction B, comprising 19%, was composed of 72 units. The analytical data presented in Table IV show that fraction A corresponded in composition to a pure glycine polypeptide ester. On the other hand, fraction B, which was heated to 135° to achieve further polymerization, seemed to contain impurities.

Reaction of Isocyanates with Polyglycine Ester and Nylon.—A 0.4-g. sample of dry polyglycine ester (B) was treated with 2 ml. of phenyl isocyanate and 5 ml. of dry pyridine at 100° for two days. The extracted reaction product weighed 0.4 g. The nitrogen content was the same as that of the starting material (Table IV).

TABLE IV

POLYMERIZATION OF GLYCINE METHYL ESTER

	Fraction A		Fraction B	
	Found, %	Calculated for 15 units, %	Found, %	Calculated for 72 units, %
Free amino -N	1.60[a]	1.58	0.34	0.34
Amino-N liberated through acid hydrolysis	25.0	23.6	19.7	24.4
Total N	23.4	23.6	23.5	24.4

[a] A three-minute reaction period was used for all amino nitrogen analyses listed in this table; after a fifteen-minute reaction period, 1.68% was found.

A 0.5-g. sample of powdered Nylon, treated in the same manner with 1.0 ml. of *o*-chlorophenyl isocyanate and 3 ml. of pyridine yielded 0.49 g. of the extracted product. The chlorine content was 1.15% (3.3 equivalents per 10^4 g. of the material, originally containing 82 peptide bonds, and 0.14 terminal amino group).

We thank L. M. White of this Laboratory for the elementary analyses.

Summary

When proteins were treated with aromatic isocyanates under anhydrous conditions and in the presence of pyridine, reaction occurred with: (1) the basic groups, including amino, guanidyl, and imidazole; (2) the acid groups, including carboxyl, thiol and phenolic; and (3) the primary amide, and probably part of the aliphatic hydroxyl groups.

Under the same conditions the peptide groups of chain molecules did not react appreciably, in contrast to the simple diketopiperazines which bind two molecules of phenyl isocyanate.

The method described by Plimmer for quantitative liberation of the primary amide, amino, and the guanidyl nitrogen by the action of nitrous acid in mineral acid was applied successfully to proteins. This reaction made possible estimations of the extent of interaction of amide groups with phenyl isocyanate.

The products of the anhydrous reaction of phenyl isocyanate with alanine and with glycine and alanine anhydrides are described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Allylic Rearrangements. XVII. The Addition of the Butenyl Grignard Reagent to Diisopropyl Ketone[1]

BY WILLIAM G. YOUNG AND JOHN D. ROBERTS[2]

Preceding studies[3,4,5] have shown that the butenyl Grignard reagent reacts with carbon dioxide and simple aldehydes and ketones to give products corresponding exclusively to the secondary form of the Grignard reagent.

In order to test the generality of the appearance of the methylvinylcarbinyl radical in the products obtained from the reaction of the butenyl Grignard reagent with carbonyl compounds, it was desirable to investigate other more complicated cases, particularly those where it might be expected that steric influences would not favor the introduction of a secondary group. In this paper we present results obtained from the reaction of diisopropyl ketone with butenylmagnesium halides.

Whitmore and George[6] have made a thorough study of the addition of a number of aliphatic Grignard reagents to diisopropyl ketone. With increasing steric hindrance in the organomagnesium halide, the yield of addition products decreased and the competing reactions of enolization and reduction became increasingly important. With isopropylmagnesium bromide no addition product could be isolated and enolization and reduction took place to the extent of 29% and 65%, respectively. This result indicates that other larger (and more sterically hindered) secondary Grignard reagents would likewise give only enolization and reduction products.

From the foregoing it was anticipated that the reaction of diisopropyl ketone with butenylmagnesium halides should be found to follow either of two possible courses: (a) if the Grignard reagent can introduce only the secondary group into carbonyl compounds, then addition should

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(1) Presented before the Division of Organic Chemistry at the New York meeting of the American Chemical Society, September, 1944.

(2) Abbott Laboratories Research Fellow, 1943–1944.

(3) Lane, Roberts and Young, THIS JOURNAL, **66**, 543 (1944).

(4) Roberts and Young, *ibid.*, **67**, 148 (1945).

(5) Ou Kuin-Houo, *Ann. chim.*, [11] **13**, 175 (1940).

(6) Whitmore and George, THIS JOURNAL, **64**, 1239 (1943); see also Conant and Blatt, *ibid.*, **51**, 1227 (1929).

fail and only the enolization and/or reduction products would be isolated; or (b) if the Grignard reagent is capable of introducing both primary and secondary groups into simple carbonyl compounds, but the methylvinylcarbinyl group is favored by a faster reaction rate, then with diisopropyl ketone the reaction leading to the introduction of this secondary butenyl group might be excluded and the mechanism leading to crotyldiisopropylcarbinol would predominate. Actually, the results were contrary to expectation. With butenylmagnesium bromide an 89% yield of addition product was obtained and of the total product approximately 85% could be considered to be derived from the secondary form of the Grignard reagent. The remaining 15% of addition product was crotyldiisopropylcarbinol (I) Butenylmagnesium chloride prepared from methylvinylcarbinyl chloride gave a somewhat different result in that at least 95% of the product contained the secondary butenyl grouping. The over-all yield was 85%.

The structure of I was established in the following ways. Ozonolysis gave acetaldehyde and a carbonyl compound (isolated as the 2,4-dinitrophenylhydrazone) which had the composition anticipated for β,β-diisopropylacrolein, indicating that in the ozonolysis or isolation procedures the anticipated β,β-diisopropyl-β-hydroxypropionaldehyde was dehydrated. Hydrogenation of I resulted in a saturated alcohol, the boiling point, refractive index and density of which were practically identical with *n*-butyldiisopropylcarbinol.

The identity of the product (II) derived from the secondary form of the Grignard reagent was not so easily established. In the first place, the material was a mixture of isomers which could not be separated by distillation through an efficient column. Hydrogenation of II gave, however, a *single* compound (III), indicating that II was a mixture of double bond but not skeletal isomers. The physical properties of III were the same as those of diisopropyl-*s*-butylcarbinol.[7] The structure of III was established by dehydration and ozonolysis of the resulting alkenes. Dehydration of III gave what appeared to be a complex mixture of alkenes and this conclusion was substantiated by the ozonolysis products. Acetaldehyde, acetone, formaldehyde, diisopropyl ketone and *s*-butyl isopropyl ketone were isolated as their derivatives. The last compound which confirms the postulated structure of the original alcohol (III) was synthesized for the comparison of the derivatives by oxidation of isopropyl-*s*-butylcarbinol. It is significant that the ozonization products of III did not contain *n*-butyraldehyde since we have found that this carbonyl compound is readily isolated from ozonolysis of the alkenes obtained from the dehydration of *n*-butyldiisopropylcarbinol.

We are at present unable to account for the fact that II appeared to be a mixture of double bond isomers; similar results have occasionally been obtained in other reactions of butenyl Grignard reagents. It may be pointed out that no further rearrangement appeared to occur on redistillation and that butenylmagnesium bromide and chloride gave substantially the same results.

The differences in behavior of aliphatic saturated Grignard reagents and butenylmagnesium halides are strikingly illustrated by the reaction with diisopropyl ketone. Butenylmagnesium halides introduce a secondary group into the ketone molecule whereas isopropylmagnesium bromide does not add.[6] The total yields of addition product exceed those obtained with saturated Grignard reagents, with the exception of methylmagnesium iodide,[6] and are better than those obtained with *s*-butyllithium.[7] These facts are significant.

Experimental

The Action of Butenylmagnesium Bromide with Diisopropyl Ketone.—To a cold dilute ethereal solution of butenylmagnesium bromide (0.35 mole) was added a solution of 40 g. (0.35 mole) of diisopropyl ketone[8] dissolved in an equal volume of ether. The mixture was stirred at room temperature overnight and was then poured onto iced ammonium chloride solution. The ethereal layer was separated, washed, and dried. The following cuts were taken during the fractionation of the reaction product through a Podbielniak Heli-Grid packed column[9] rated at 40–60 plates.

Cut	Temp., °C.	Press., mm.	Wt., g.	$n^{20}D$
1–5	43.1– 71.9	125	7.0	1.4185–1.4140
6–7	52.3–103.9	50	1.7	1.4155–1.4415
8–10	103.8–116.0	50	3.9	1.4545–1.4587
11–13	116.0–118.9	50	38.2	1.4603–1.4604
14–16	118.9–123.3	50	2.5	1.4613–1.4628
17	123.3–123.3	50	2.8	1.4631
18[a]	103–105	20	3.0	1.4640
Residue			1.4	

[a] Holdup, distilled from a small Claisen flask.

Fractions 1–7 were a mixture of octadienes and diisopropyl ketone. Fractions 8–10 were impure undecenol and Fractions 11–14 corresponded to the secondary form of the Grignard reagent. Cuts 17 and 18 were considered to be crotyldiisopropylcarbinol. Part of Fraction 12 was refractionated at a high reflux-ratio. Cuts were taken from 114.2–115.6 (50 mm.) and these showed $n^{20}D$ 1.4546–1.4607. Calculation and summation of the contribution of each fraction to the total refractive index (assuming perfect solutions and mol-per cent. equal to weight-per cent.) gave $n^{20}D$ 1.4600 and as the original index of the combined material was 1.4603 little, if any, isomerization could have taken place on redistillation.

The structure of the higher-boiling product (I) was established by ozonolysis and hydrogenation. Fraction 18 (0.8 g.) was ozonized in 5 ml. of methylene chloride[10] at −70°. The method of Whitmore and Church[11] was used for reduction and isolation of the products. Acetaldehyde was isolated as the methone derivative, m. p. 142.5–143.5°. Steam distillation of the reduction products of the ozonide gave a trace of formaldehyde (methone deriva-

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[7] Young and Roberts, This Journal, **66**, 1444 (1944).

[8] Pure material was generously supplied by Dr. F. C. Whitmore of the Pennsylvania State College.

[9] Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **13**, 639 (1941).

[10] Henne and Perilstein, This Journal, **65**, 2183 (1943).

[11] Whitmore and Church, *ibid.*, **54**, 3710 (1932).

tive, m. p. 188.5–190.5°) and an oil with a strong terpene-like odor which formed a bright-red 2,4-dinitrophenylhydrazone, m. p. 151.5–153° after crystallization from alcohol. This hydrazone had the composition $C_{15}H_{20}O_4N_4$ and was probably the derivative of β,β-diisopropylacrolein. *Anal.* Calcd. for $C_{15}H_{20}O_4N_4$: C, 56.23; H, 6.29; N, 17.50. Found: C, 56.44; H, 6.16; N, 17.32 (analysis through the courtesy of A. J. Haagen-Smit, California Institute of Technology.)

Fraction 17 (2.08 g.) was hydrogenated in ethanol over platinum oxide. The absorption of hydrogen was 97% after an hour. Distillation gave 1.70 g. (82%) of saturated alcohol; b. p. 104° (25 mm.), $n^{20}\text{D}$ 1.4479, d^{20}_4 0.859. The corresponding properties of *n*-butyldiisopropylcarbinol are b. p. 121° (50 mm.), $n^{20}\text{D}$ 1.4479, d^{20}_4 0.860. This compound was prepared in 40% yield by the reaction of *n*-butylmagnesium bromide with diisopropyl ketone. Enolization and reduction amounted to 9 and 50%, respectively.[6]

The carbon skeleton of II was established by hydrogenation and degradation of the resulting saturated alcohol. Fraction 12 (18.3 g.) was hydrogenated in methanol over platinum oxide. The absorption of hydrogen was 92% of the theoretical after twenty minutes. The hydrogenation product (III) was fractionated through an efficient column and the following cuts were taken:

Fraction	Temp., °C.	Press., mm.	Wt., g.	$n^{20}\text{D}$
1	117.1	50	0.2	1.4481
2–5	118.7–120.1	50	14.3	1.4522–1.4520
6[a]	120	50	1.5	1.4521
Residue			1.0	

[a] Holdup, distilled from a small Claisen flask.

The combined material of Fractions 2–6 showed $n^{20}\text{D}$ 1.4520, d^{20}_4 0.868; yield 15.8 g. (86%). The physical properties of *s*-butyldiisopropylcarbinol[7] are b. p. 121.9° (50 mm.), $n^{20}\text{D}$ 1.4518, d^{20}_4 0.868.

The dehydration of III (12.4 g.) proceeded readily on slow distillation with iodine. The yield of alkenes was 9.4 g. (82%); b. p. 77–87° (37 mm.), $n^{20}\text{D}$ 1.4413. Absorption of ozone by the alkenes (4.0 g.) in methylene chloride at −70° was slow and considerable unused ozone was apparent in the effluent gases. After two hours the solvent was evaporated and the ozonide reduced.[11] Acetaldehyde, formaldehyde, acetone and diisopropyl ketone were isolated and identified in the customary manner. A carbonyl compound boiling above diisopropyl ketone was isolated as the 2,4-dinitrophenylhydrazone, m. p. 70–72° after crystallization from petroleum ether. This hydrazone did not depress the melting point of the corresponding derivative of isopropyl *s*-butyl ketone (see below).

Butenylmagensium Chloride and Diisopropyl Ketone.—From 0.38 mole of butenylmagnesium chloride prepared from methylvinylcarbinyl chloride (b. p. 62.5–63.0, $n^{20}\text{D}$ 1.4150) and 43 g. (0.38 mole) of diisopropyl ketone were obtained (other than octadienes and recovered ketone) 46.8 g. (77%) of undecenols corresponding to the secondary form of the Grignard reagent; b. p. 115.4–115.8° (50 mm.), $n^{20}\text{D}$ 1.4588–1.4607. The column holdup afforded 4.2 g. (17%) of material, b. p. 119.5–127.0° (50 mm.), $n^{20}\text{D}$ 1.4623, which was probably at least half crotyldiisopropylcarbinol. The over-all yield was 84% and of this at least 94% corresponded to the secondary Grignard reagent.

Hydrogenation of the secondary product (17 g.) gave, after fractionation, 15.8 g. (93%) of diisopropyl-*s*-butylcarbinol; b. p. 119.7–120.0° (50 mm.), $n^{20}\text{D}$ 1.4520.

Isopropyl *s*-Butyl Ketone.—A mixture of 11.3 g. (0.087 mole) of isopropyl *s*-butylcarbinol[12] with a solution of 11.7 g. of potassium dichromate and 17.0 g. of concentrated sulfuric acid in 100 ml. of water was heated to 40° with stirring for thirty-six hours. The mixture was diluted with water and extracted with ether. The extracts were dried over "Drierite" and fractionated. The yield of ketone was 7.7 g. (68%); b. p. 65.5° (50 mm.), $n^{20}\text{D}$ 1.4080.

Anal. Calcd. for $C_8H_{16}O$: C, 74.93; H, 12.58. Found: C, 74.77; H, 12.9.

The 2,4-dinitrophenylhydrazone was obtained as long yellow needles from alcohol, m. p. 69–71°.

Anal. Calcd. for $C_{14}H_{20}O_4N_4$: C, 54.53; H, 6.53. Found: C, 54.59; H, 6.64.

Summary

1. Butenylmagnesium bromide reacted with diisopropyl ketone to give an 89% yield of addition product. Of the total product 85% could be considered to correspond to the secondary form of the Grignard reagent while 15% was crotyldiisopropylcarbinol.

2. Butenylmagnesium chloride with diisopropyl ketone gave an 85% yield of addition product, of which at least 94% could be considered to be derived from the secondary form of the Grignard reagent.

3. Butenylmagnesium halides are the only Grignard reagents known at the present time which will introduce a secondary group into diisopropyl ketone.

4. The yields of addition products obtained with butenyl Grignard reagents and diisopropyl ketone appear to surpass those obtainable with any saturated aliphatic organomagnesium halides with the exception of methylmagnesium iodide.

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[12] Details of the preparation of this compound will be described in a forthcoming communication.