2,3,6-trimethylglucose. In every respect the two specimens were identical in composition and properties; yield 1.8 g.

Acknowledgment is made to the Carnegie Trust for a Research Fellowship awarded to one of us.

Summary

1.   The constitution of 2,3-dimethylglucose has been verified and the sugar has been converted by a sequence of synthetical reactions into 2,3,6-trimethylglucose.

2.   These reactions are based on the fact that while 2,3-dimethylglucose gives a di-nitrate, only the nitrate group in position 6 is replaceable by iodine.   It was therefore possible to restrict the introduction of the third methyl group to position 6 as positions 4 and 5 were masked.

St. Andrews, Scotland

THE REDUCING ACTION OF THE GRIGNARD REAGENT AND THE SYNTHESIS OF TERTIARY ALIPHATIC CARBINOLS

By A. H. Blatt and Julius F. Stone, Jr.

It was recently shown[1] that a few aliphatic aldehydes and a number of aliphatic ketones were more or less completely reduced to the corresponding primary and secondary alcohols by treatment with certain Grignard reagents.   These reductions were roughly correlated with the size and complexity of the alkyl groups present in the carbonyl compound and the reagent and the limits of usefulness of the Grignard reagent in synthesizing aliphatic carbinols were pointed out.

The present work was undertaken in order to secure additional information about the effect of branched chain alkyl groups on the reaction between aliphatic ketones and the Grignard reagent.   By the use of a properly chosen series of isomeric ketones and reagents we hoped to learn not only the exact effect of branching the alkyl groups but also, using substances of equal complexity, to learn the effect of the location of the branched groups. We have, therefore, treated each of the three ketones, di-propyl ketone, propyl isopropyl ketone and di-isopropyl ketone, with propyl- and iso-propylmagnesium bromides.   Some of these reactions had been done before but we found it necessary to repeat certain of them because the reported results were either contradictory or incomplete.   We followed in our Grignard reactions what we prefer to term the normal procedure: the addition of the carbonyl compound to an excess of reagent free from excess magnesium.   Using this procedure completeness of reaction is as-

[1] Conant and Blatt, This Journal, 51, 1227 (1929).

sured and any reduction observed can be ascribed definitely to the reagent. The results of our experiments are shown in the table.

TABLE I

RESULTS OF EXPERIMENTS

	Ketone	Reagent	Addition	Reduc-tion	Enoliza-tion	Total
A	$CH_3CH_2CH_2COCH_2CH_2CH_3$	$CH_3CH_2CH_2MgBr$	54^2	24	..	78
B	$CH_3CH_2CH_2COCH_2CH_2CH_3$	$(CH_3)_2CHMgBr$	$44^{2,3}$	5	15	64
C	$CH_3CH_2CH_2COCH(CH_3)_2$	$CH_3CH_2CH_2MgBr$	63	17	..	80
D	$CH_3CH_2CH_2COCH(CH_3)_2$	$(CH_3)_2CHMgBr$	17	49^4	..	66
E	$(CH_3)_2CHCOCH(CH_3)_2$	$CH_3CH_2CH_2MgBr$	43^2	34	..	77
F	$(CH_3)_2CHCOCH(CH_3)_2$	$(CH_3)_2CHMgBr$	0^1	80	..	80

The first and second columns of the table give the ketones and reagents used. The next two columns represent the percentages of the original ketone which appeared as addition and reduction product, respectively. The fifth column shows the percentage of the original ketone which was recovered. In view of the work of Grignard[5] and Kohler[6] this material was doubtless present in the reaction mixture as the enolic magnesium derivative. The last column shows the percentage of the original ketone accounted for.

The effect on the reaction between the Grignard reagent and ketones, of branching the alkyl groups present is clearly revealed by the foregoing table. Reactions A, C and E show the effect of branching the alkyl groups (increasing their complexity) in the ketones. This same effect is shown by reactions B, D and F while the comparisons of reactions B with A, D with C, and F with E show the effect of branching the group in the reagent. From these comparisons it can be seen at the outset that it is far more safe to speak of the effect of branched groups in decreasing addition than in increasing reduction. While it is, of course, generally true that reduction increases as the number of branched groups increases the exceptions are so numerous as to emphasize strongly the view previously put forward[7] that reduction is only one of several reactions which come into prominence as addition falls off. The factors deciding which one of these several reac-

[2] These reactions were also done by Stas, (a) *Bull. soc. chim. Belg.*, **34**, 188 (1925); (b) *ibid.*, **35**, 379 (1926), who reported for A, first 37% addition and 10% reduction and later 60% addition and 20% reduction. For B, Stas reported addition only, giving no yield. For E, he reported 30% addition and 30% reduction.

[3] In this reaction we obtained a considerable amount of high-boiling material, apparently condensation products, which we have not included in the above figures.

[4] A sharp separation of reduction and enolization products could not be effected in this experiment.

[5] Grignard and Savard, *Compt. rend.*, **179**, 1573 (1924); *Bull. soc. chim. Belg.*, **36**, 97 (1927).

[6] Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927).

[7] Ref. 1, p. 1231.

tions (reduction, enolization, condensation) will predominate in a given case are far too complex to allow predictions to be made on the basis of the experimental evidence so far available.

More interesting because more novel and clear-cut is the effect on the reaction of the relative position of the branched groups, *i. e.*, whether present in the ketone or in the reagent. It will be observed that reaction C and reaction B lead to the same addition product. Similarly, the addition product from reaction E is identical with that from reaction D. In C and E straight chain reagents are used, in B and D branched chain reagents. With the straight chain reagents high yields of addition product and clean reactions result; with the branched reagents the yields of addition product are low and the reactions are complicated by numerous side processes. The practical significance of this observation is at once apparent: in the synthesis of tertiary aliphatic carbinols containing branched and straight chain alkyl groups and where the branches are in the α-position to the carbinol carbon atom, one should treat a branched chain ketone with a Grignard reagent prepared from a primary straight chain alkyl halide.

The observations most closely related to our own work which we have been able to find are some experiments of Rheinboldt and Roleff,[8] who showed that when certain phenyl alkyl ketones were treated with phenylmagnesium bromide, the result was addition but that when benzophenone was treated with the corresponding alkylmagnesium halide considerable reduction took place. Since phenylmagnesium bromide is not capable of giving the same type of reduction as alkylmagnesium halides, these experiments are not directly comparable with ours. However, it would follow from the work of Rheinboldt and Roleff and that of Blicke and Powers[9] that the preparation of diphenyl alkyl carbinols of any complexity should be carried out by the addition of phenylmagnesium bromide to the phenyl alkyl ketone rather than by the addition of an alkylmagnesium halide to benzophenone.

Experimental

Since the same procedure was employed in all our experiments we shall, in order to save space, describe the procedure at this point and give under the individual reactions only the necessary factual details. Each Grignard reagent employed was prepared in the usual fashion from 1.2 moles each of magnesium and alkyl halide and 500 cc. of ether. After standing overnight the reagent was decanted, through a glass-wool filter, from the excess magnesium, then chilled in an ice- and salt-bath while to it was added

[8] Rheinboldt and Roleff, *Ber.*, **57**, 1921 (1924); *J. prakt. Chem.*, [2] **109**, 175 (1925).

[9] Blicke and Powers, THIS JOURNAL, **51**, 3378 (1929).

0.5 mole of ketone in 100 cc. of ether. The reagent was stirred mechanically during this addition, which required about one hour. No evolution of gas occurred at this stage nor was there any color developed or precipitate formed. The ice-bath was then removed and after stirring for fifteen minutes the reaction mixture was boiled for thirty minutes or until the evolution of gas had ceased. Decomposition of the reaction mixture was then effected by pouring it onto ice to which had been added a slight excess over the theoretical amount of concd. sulfuric acid. The ether and water layers which were then separated were colorless. The water layer was shaken out twice with ether and these extracts were added to the original ether layer. The combined ether extracts were washed with water, sodium carbonate solution and water, then dried over sodium sulfate. Next the ether was removed on the steam-bath and the residual liquid subjected to a series of fractionations at atmospheric or reduced pressure according to the properties of the products.

Propylene was evolved during the reactions as was shown by absorbing it in bromine water and identifying the resulting propylene dibromide by its boiling point, 134–140°.

The ketones employed were prepared by the usual procedure, treatment of an aldehyde with a Grignard reagent followed by oxidation of the secondary alcohol so produced. All the ketones used as well as their reduction products, the secondary alcohols, and their addition products, the tertiary alcohols, have been prepared and described before. Consequently our identification of the reaction products was made by means of their boiling points.

It will be noted that in each of the reactions with the exceptions of B and D, approximately 78% of the starting material was accounted for. The losses of material were due in part, of course, to the difficulty of making a complete separation of the ether and water layers when the reaction mixtures were decomposed. They were due, also, however, to the fact that intermediate fractions in the purification of the reaction products were not counted in estimating the percentage yields. The larger losses in reactions B and D were due to the many transfers occasioned by the fact that the separation of the reaction products required numerous fractionations. No high order of accuracy is claimed for the experiments. In a typical case, however, repetition of an experiment gave essentially identical results.

In the individual experiments next to be described only the significant fractions are given. The forerunnings, intermediate fractions and residues have been omitted.

A. Di-propyl Ketone and Propylmagnesium Bromide.—From 57 g. of ketone there was obtained 14 g. of di-propylcarbinol boiling at 150–156° and 43 g. of tri-propylcarbinol[10] boiling at 190–193°.

B. Di-propyl Ketone and Isopropylmagnesium Bromide.—From 57 g. of starting material there was recovered 8.9 g. of di-propyl ketone, boiling at 142–144°. In addition we obtained 2.7 g. of di-propylcarbinol, boiling at 153–155°, and 35.1 g. of di-propylisopropylcarbinol[2b] boiling at 110° (50 mm.). There was also obtained 6.6 g. of material which boiled at about 130° at 10 mm., apparently a condensation product.

C. Propyl Isopropyl Ketone and Propylmagnesium Bromide.—From 57 g. of ketone we obtained 10 g. of propylisopropylcarbinol, 140–146°, and 50.1 g. of di-propylisopropylcarbinol, 110° (50 mm.).[2b]

D. Propyl Isopropyl Ketone and Isopropylmagnesium Bromide.—In this reaction we were unable to effect a separation of the enolization and reduction products. From 57 g. of ketone we obtained 28.4 g. of material which boiled from 137–147° and was apparently a mixture of ketone and secondary alcohol. The addition product, propyldiisopropylcarbinol[2b] amounted to 14 g. and boiled at 100° at 50 mm. There was also a small amount, 3.5 g., of high-boiling condensation products. Similar results were ob-

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[10] Beilstein–Prager–Jacobson, Julius Springer, Berlin, 1920, Vol. I, p. 426.

tained in a check experiment where it appeared that the low-boiling material was chiefly reduction product.

E. Di-isopropyl Ketone and Propylmagnesium Bromide.—From 57 g. of ketone we obtained 19.6 g. of di-isopropyl carbinol boiling at 134–138° and 34.3 g. of propyl di-isopropyl carbinol[2b] boiling at 100° (50 mm.).

Summary

From a study of the reaction between certain aliphatic ketones and some alkylmagnesium halides it is pointed out that there is no definite and exact correlation between an increase in the complexity of the alkyl groups present and the amount of reduction observed.   Further it is shown that the synthesis of tertiary aliphatic carbinols containing both straight and branched chain alkyl groups and where the branches are in the α-position to the carbinol carbon atom, should be carried out by the interaction of branched chain ketones and primary straight chain Grignard reagents.

BUFFALO, N. Y.

THE DETERMINATION OF THE IONIZATION CONSTANTS OF GUANIDINE AND SOME OF ITS ALKYLATED DERIVATIVES[1]

BY TENNEY L. DAVIS AND ROBERT C. ELDERFIELD[2]

Guanidine seemingly occupies a unique position among organic bases, for, with the possible exception of the quaternary ammonium and the substituted iodonium bases, it alone approximates the strong fixed alkalies in basic strength.   Notwithstanding, the study of its ionization appears to have been largely neglected, while the extent to which the presence of substituents influences its dissociation has attracted no attention whatsoever.   In the course of other work which will be reported shortly, information regarding this point was desired, and the results of such an investigation are here presented.

Ostwald[3] made careful measurements of the conductivity of aqueous solutions of guanidine, but there appears to have been no calculation of an ionization constant from these data.   Such a calculation shows that guanidonium hydroxide apparently behaves as a strong base.   Bredig[4]