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Highly-Branched Compounds. The Preparation of Triisopropylcarbinol and Diisopropyl-*s*-butylcarbinol

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Studies of organic compounds in which the carbon chain has one or more branches have been of great interest, particularly in relation to the phenomena of steric hindrance and molecular rearrangements. The extensive investigations of Whitmore and co-workers[2] on the chemistry of the neopentyl group afford an outstanding example of the differences in reactivity and reactions which are exhibited in the more highly-branched compounds.

In the past, the principal bar to the study of many highly-branched substances has been the difficulties involved in their preparation. For example, an investigation initiated by Conant and Blatt[3] with the intention of synthesizing compounds containing the triisopropylmethyl group was abandoned because of the failure of isopropylmagnesium bromide to undergo normal addition to diisopropyl ketone. Subsequently, in a study of the reactions of diisopropyl ketone with a variety of Grignard reagents, Whitmore and George[4] showed that when the steric nature of the reagent was such that the rate of the addition reaction was decreased, the slower reactions of enolization and reduction occurred to an extent depending on the structure of the reactant. With isopropylmagnesium bromide they report 29% enolization, 65% reduction and no addition. Aliphatic alcohols of the triisopropylcarbinol type have not been previously reported in the literature.

As part of another investigation in progress in this Laboratory, it was desirable to prepare diisopropyl-*s*-butylcarbinol. It is well known that lithium compounds generally undergo addition reactions more rapidly than their magnesium analogs and, therefore, the reaction of *s*-butyllithium with diisopropyl ketone was investigated. Although the conversion of *s*-butyl chloride to the corresponding lithium compound in petroleum ether[5] was unsatisfactory and much unreacted lithium remained, diisopropyl-*s*-butylcarbinol was isolated in 30% yield and 57% of the diisopropyl ketone was recovered. No significant amounts of diisopropylcarbinol were isolated. Triisopropylcarbinol was prepared similarly in 19% yield. Recovered diisopropyl ketone amounted to 67% and no diisopropylcarbinol was isolated.

In another preparation of triisopropylcarbinol where the solution of the addition complexes was refluxed for several hours before hydrolysis, a somewhat different result was obtained in that diisopropylcarbinol (17%) was obtained. In diethyl ether the yield of triisopropylcarbinol was 5% and the reduction products amounted to 36%. Isopropylmagnesium bromide suspended in petroleum ether gave, with diisopropyl ketone, 68% enolization, 21% reduction and no addition.

The distillation residues afforded small amounts of 3,4 - diisopropyl - 2,5 - dimethylhexandiol - 3,4 which may have resulted from a bimolecular reduction of diisopropyl ketone by the excess of metallic lithium. This compound has been previously reported[6] as the product resulting from the bimolecular reduction of diisopropyl ketone by sodium in diethyl ether.

The structure of the triisopropylcarbinol was confirmed by dehydration and ozonolysis of the resulting alkenes. Dehydration over copper sulfate gave what appeared to be an inseparable mixture of alkenes, possibly through rearrangement of the double bond. The product could not be hydrogenated over platinum oxide at room temperature. Ozone was absorbed but slowly at −70° and the only isolable carbonyl compounds resulting from the reduction of the ozonide were acetone, diisopropyl ketone and traces of formaldehyde.

A detailed structure proof of diisopropyl-*s*-butylcarbinol will be presented in a later communication. For the present, only a comparison will be made of the physical properties of the known members of the series (Table I).

TABLE I

PHYSICAL PROPERTIES OF $R[(CH_3)_2CH]COH$

R	B. p., °C.	Press., mm.	$n^{20}D$	d^{20}_4	Ref.
n-Bu	121	50	1.4479	0.860	7
s-Bu	122	50	1.4520	0.868	This paper
i-Bu	140	125	1.4426		4
n-Pr	132	125	1.4445		4
i-Pr[a]	108	50	1.4480	0.874	This paper

[a] Melting point, −7°.

A preliminary study of the chemical properties of triisopropylcarbinols indicates that they behave much as *t*-butyldiethylcarbinol which was investigated by Bartlett and Knox.[8] Thus, dehydration occurs readily and halides are easily formed with hydrogen chloride. These facts support the conclusion of Bartlett that steric hindrance in tertiary alcohols and their derivatives does not inhibit reactivity (even if the back side

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(1) Abbott Laboratories Research Fellow, 1943–44.

(2) Whitmore and co-workers, THIS JOURNAL, **54**, 3131 (1932); **55**, 4161 (1933); **61**, 1585, 1586, 1591 (1939).

(3) Conant and Blatt, *ibid.*, **51**, 1227 (1929).

(4) Whitmore and George, *ibid.*, **64**, 1239 (1942).

(5) Gilman, Langham and Moore, *ibid.*, **62**, 2327 (1940).

(6) Nazarov, *Compt. rend. acad. sci. U. R. S. S.*, **4**, 288 (1934) [*C. A.*, **29**, 2914 (1935)].

(7) Unpublished studies in This Laboratory, see also Ref. 3.

(8) Bartlett and Knox, THIS JOURNAL, **61**, 3184 (1939).

of the central carbon atom is virtually inaccessible to the reagents) provided that the molecule may assume the planar configuration required for the existence of a stable carbonium ion.

Experimental Part

Materials.—Lithium metal was pressed and handled according to the convenient procedure of Fieser and Hershberg.[9] Isopropyl chloride (b. p. 34.3–35.0°) and *s*-butyl chloride (b. p. 67–68°) were prepared by the treatment of the respective alcohols with zinc chloride and hydrochloric acid.[10] Diisopropyl ketone which had been fractionated through a 100-plate column was used without further treatment.[11] Petroleum ether (30–60°) was washed several times with concentrated sulfuric acid and fractionated, retaining the material boiling at 35–37°.

Diisopropyl-*s*-butylcarbinol.—A solution of *s*-butyllithium was prepared under a nitrogen atmosphere in 100 ml. of petroleum ether from 5.3 g. (0.76 gram atom) of lithium and 35 g. (0.38 mole) of *s*-butyl chloride. The reaction proceeded quite slowly and even after stirring overnight much excess lithium was present. To the above preparation was added a solution of 43.5 g. (0.38 mole) of diisopropyl ketone dissolved in an equal volume of petroleum ether. After an hour the mixture was decomposed with iced ammonium chloride solution and worked up in the usual way. Fractionation of the high-boiling material through a 0.8 × 45 cm. Podbielniak Hyper-Cal Heli-Grid[12] packed column rated (at the reflux rates employed) at 40–60 theoretical plates gave the following cuts.

Frac.	B. p., °C.	Press., mm.	Wt., g.	n^{20}D
2- 6	65.4- 73.4	125	25.7	1.3897-1.4003
7	73.4-140.0	125	3.0	1.4260
8- 9	115.4-120.7	50	3.2	1.4508-1.4513
10-13	120.7-121.5	50	17.5	1.4518-1.4520

Fractions 2–6 were diisopropyl ketone (57%) and 9–13 diisopropyl-*s*-butylcarbinol (30%).

Anal. Calcd. for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 76.56; H, 14.25.

This distillation residue solidified and two crystallizations from petroleum ether (32–35°) gave 0.25 g. of solid; m. p. 89.5–90.5°. This material had the composition of 3,4-diisopropyl-2,5-dimethylhexandiol-3,4.

Anal. Calcd. for $C_{14}H_{30}O_2$: C, 72.98; H, 13.13. Found: C, 73.21; H, 12.97.

Diisopropyl-*s*-butylcarbinol was readily reactive to dry hydrogen chloride at 0° with the separation of an aqueous phase. The product, after being washed and dried, gave a rapid precipitate with alcoholic silver nitrate.

Triisopropylcarbinol.—The procedure was the same as in the preceding preparation and 7.0 g. (1.0 gram atom) of lithium, 40 g. (0.51 mole) of isopropyl chloride, 57 g. (0.5 mole) of diisopropyl ketone and 150 ml. of petroleum ether were employed. Before adding the reaction mixture to iced ammonium chloride solution, the unreacted lithium which was heavily encrusted with lithium chloride was filtered, carefully decomposed with ice water and the resulting lithium hydroxide titrated with standard acid. The excess metal so determined amounted to 0.30 gram atom.

Fractionation of the products gave: diisopropyl ketone, 38.8 g. (68%), n^{20}D 1.4000–1.4009; intermediate cuts, 3.3 g., n^{20}D 1.4150–1.4452; and triisopropylcarbinol, 14.5 g. (19%), b. p. 106.6–108.0° (50 mm.), n^{20}D 1.4476–1.4480. The yield of triisopropylcarbinol was 26% on the basis of lithium consumed.

Anal. Calcd. for $C_{10}H_{22}O$: C, 75.87; H, 14.01. Found: C, 75.72; H, 14.10.

In a similar experiment where the preparation of isopropyllithium was refluxed for three days and after the addition of diisopropyl ketone refluxed for three hours, the following substances were isolated: unreacted lithium (8%), triisopropylcarbinol (19%), 3,4-diisopropyl-2,5-dimethylhexandiol-3,4 (8%), diisopropyl ketone (39%) and diisopropylcarbinol (17%).

Isopropylmagnesium bromide (0.25 mole) which was prepared in ether and, after evaporation of the solvent, heated under reduced pressure at 100° for two hours was suspended in petroleum ether and the equivalent amount of diisopropyl ketone added. Much olefin-containing gas was evolved. Diisopropylcarbinol (68%) and diisopropyl ketone (21%) were isolated from the reaction mixture. No triisopropylcarbinol was detected.

Dehydration of the carbinol (9.2 g.) by refluxing at 300 mm. over anhydrous copper sulfate gave after fractionation 6.7 g. (83%) of alkenes; b. p. 84.0–88.0° (100 mm.), n^{20}D 1.4345–1.4375. Dehydration over iodine as catalyst was unsatisfactory.

Anal. Calcd. for $C_{10}H_{20}$: C, 85.62; H, 14.37. Found: C, 85.77; H, 14.59.

The alkenes (2.0 g.) were dissolved in dichlorodifluoromethane[13] (Freon) and subjected to a stream of ozonized oxygen at −70°. The absorption of ozone was slow and the reaction was allowed to continue for two hours. The method of Whitmore and Church[14] was used for reduction of the ozonide and isolation of the products. Diisopropyl ketone, acetone and traces of formaldehyde were identified through the customary derivatives and mixed melting points.

The alkenes were resistant to low pressure hydrogenation in ethyl alcohol at room temperature over platinum oxide catalyst.

Summary

The preparation of triisopropylcarbinol and diisopropyl-*s*-butylcarbinol has been accomplished by the addition of the appropriate lithium alkyls to diisopropyl ketone. These alcohols, which are the first of their type to be prepared, behave as typical tertiary alcohols, thus being readily dehydrated and reactive to hydrogen chloride.

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(9) Fieser and Hershberg, This Journal, **59**, 396 (1937).

(10) "Organic Syntheses," Coll. Vol. I, p. 142 (second edition).

(11) This material was generously supplied by Dr. F. C. Whitmore of The Pennsylvania State College.

(12) Podbielniak. *Ind. Eng. Chem., Anal. Ed.*, **13**, 639 (1941).

(13) Dichlorodifluoromethane is a valuable solvent for ozonolysis as it is inert to the reagent and is easily removed under reduced pressure. The use of this material was suggested by Dr. T. L. Jacobs of This Laboratory.

(14) Whitmore and Church, This Journal, **56**, 176 (1934).