[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

# The Supposed Enolizing Power of Organic Magnesium Compounds

BY E. P. KOHLER AND DONALD THOMPSON

In a paper entitled "Researches on the Enolization of Ketones," Grignard and Blanchon[1] described the formation of a number of halomagnesium enolates by the action of isopropylmagnesium bromide on saturated ketones. In proof that their magnesium derivatives were enolates, they converted them into acetates with acetyl chloride and hydrolyzed the acetates to keto-enol mixtures in which they determined the enol content by the method of Job and Reich.[2]

Since the formation of an acetate by the action of acetyl chloride on a halomagnesium enolate which has no substituent in the alpha position is contrary to our experience,[3] we decided to repeat one of the experiments of Grignard and Blanchon in the hope of discovering the reason for the discrepancy, selecting for this purpose the reaction with cyclohexanone because cyclohexenyl acetate can be prepared by a method that leaves no doubt as to its structure.[4]

We began by operating as nearly as possible in accordance with the directions of the authors, but although we repeated their experiment a number of times, employing carefully purified cyclohexanone and isopropyl bromide, we were unable to isolate any cyclohexenyl acetate. By careful distillation under diminished pressure it was possible to secure a fraction which boiled approximately at the specified temperature, but the boiling point at the ordinary pressure (174–175°) and an analysis showed that this fraction was almost pure cyclohexyl acetate.

*Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 68.1; H, 10.1.

We then prepared pure cyclohexenyl acetate by the method of Mannich and Hancu and hydrolyzed it as directed by Grignard and Blanchon. But here also, in spite of many attempts, we were unable to duplicate their results; our hydrolysis product was always pure cyclohexanone.

Finally, in order to determine the primary products we added cyclohexanone to isopropylmagnesium bromide as directed, but decomposed the resulting magnesium compounds with ammonium chloride in the ordinary manner. We thus obtained two liquids, the one boiling at 160–161°, the other at 115–116° (2 mm.). The lower boiling liquid was identified as cyclohexanol by its boiling point, its index of refraction ($n^{20}_D$ 1.4660) and the melting point of its phenyl urethan (82.5°). The higher boiling frac-

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(1) Grignard and Blanchon, *Bull. soc. chim.*, [4] **49**, 23 (1931).

(2) Job and Reich, *ibid.*, [4] **33**, 1414 (1923).

(3) Kohler and Baltzly, THIS JOURNAL, **54**, 4015 (1932); Kohler and Peterson, *ibid.*, **55**, 1073 (1933).

(4) Mannich and Hancu, *Ber.*, **39**, 1594 (1906); **41**, 564 (1908).

tion was identified as cyclohexylidene cyclohexanone by an analysis and a comparison of its semicarbazone (m. p. 177°) with that of an authentic sample. The yields were 34 g. or 68% of cyclohexanol and 11.6 g. or 26% of cyclohexylidene cyclohexanone from 49 g. of the ketone.

From the foregoing account it is evident that under the conditions favored by Grignard and Blanchon, at least 94% of the product of the reaction between cyclohexanone and isopropylmagnesium bromide is composed of substances which are not due to enolization but to reduction and to condensation. Lower temperatures, which according tot he French authors are less favorable to enolization, are in reality less favorable to reduction, the reduction product being in part replaced by the normal addition product. Thus at −5° the yield of cyclohexanol was only 28%.

In view of these results we are compelled to conclude that Grignard and Blanchon were misled by the method of Job and Reich, and that they mistook cyclohexyl acetate for cyclohexenyl acetate, cyclohexanol for cyclohexenol. Grignard reagents containing secondary and tertiary hydrocarbon residues frequently act as condensing and reducing agents, but we can find no evidence that they are more effective than others in inducing enolization, and we also fail to find any evidence that any Grignard reagents can convert mono ketones into enolates unless the hindrance to addition is prohibitive.

## Summary

An examination of the reaction between isopropyl magnesium bromide and cyclohexanone showed that Grignard and Blanchon must have mistaken reduction for enolization.

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RECEIVED MAY 29, 1933
PUBLISHED SEPTEMBER 5, 1933

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

# Some New Local Anesthetics Containing the Piperazine Ring

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As piperazine can be regarded as a double secondary amine, it seemed of interest to prepare and study a series of esters of piperazine-dialkanols, which could be regarded as compounds of the procaine type and therefore would be expected to possess local anesthetic activity. The only compound of this type noted in the literature was β-1,4-piperazine-diethyl benzoate which was described by Pyman. He stated that this substance shows[1] marked local anesthetic activity but is quite toxic.

In the present investigation, β-1,4-piperazine-diethanol and γ-1,4-piperazine-dipropanol were prepared by the condensation of piperazine

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[1] Pyman, *J. Chem. Soc.*, **93**, 1802 (1908).