[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

# The Enolizing Action of Methylmagnesium Iodide upon Hindered Ketones[1]

BY LEE IRVIN SMITH AND CYRUS GUSS[2]

The reaction between ketones and Grignard reagents most frequently consists in addition of the reagent to the carbonyl group. However, when the carbonyl group or the Grignard reagent is hindered by the accumulation of substituents near the functional group, speed of the addition reaction is reduced greatly, and under these circumstances time is available for other slower reactions to occur. The chief of these slower reactions are enolization, condensation and reduction.[3] Acetomesitylene has been studied rather extensively as an example of a hindered ketone in which the ordinary reactions involving addition to the carbonyl group are decreased in velocity to the point at which the slower, "abnormal" reactions make themselves felt. Thus the oxime cannot be made by the ordinary procedures;[4] the ketone is completely resistant to the action of alkalies, but is cleaved to the hydrocarbon (mesitylene) and acetic acid by the action of phosphoric acid,[5] in contrast to the behavior of acetophenone, which is cleaved to benzoic acid; and the ketone does not undergo the haloform reaction.[6]

Kohler, Stone and Fuson[7] using their "Grignard machine," found that acetomesitylene was completely enolized by methylmagnesium iodide, giving an iodomagnesium enolate together with an equivalent amount of methane, a result which was verified in a more extensive study of the reaction by Kohler and Baltzly.[4d] That enolization of ketones by Grignard reagents is primarily a function of hindrance in the ketone and that branching of the chain in the reagent is of relatively minor importance in this reaction, was shown by Kohler and Thompson.[8]

In order to extend and amplify the information on enolization of hindered ketones by Grignard reagents, the behavior of thirteen aceto- and diacetopolymethylbenzenes toward methylmagnesium iodide has been examined. The results are given in Table I.

The compounds were dissolved in xylene and analyses were made in a "machine" built essentially after the pattern of the one used by Kohler and his collaborators[7,9] and the procedure was essentially that used by them. The monoacetyl compounds were fairly easily handled, but the diacetyl compounds gave rise to complications due to the insolubility of the iodomagnesium derivative in the solvent. In such cases, the amount of xylene, as well as the time during which the reaction mixture was heated, had to be increased considerably before consistent results could be obtained. When water was added in the second part of the analysis it was also necessary to prolong the time of heating. Moreover, cautious shaking of the reaction chamber during both the first part of the analysis and the later decomposition by water was absolutely necessary. A correction factor, due to gas (nitrogen) dissolved in the reagent and to moisture which could not be removed from the apparatus, had to be introduced into the calculations. The correction, experimentally determined, amounted to 1.52 cc. Consistent values for the amount of

TABLE I

GRIGNARD ANALYSES OF ACETOPOLYMETHYLBENZENES

| Ketone | Active H moles per mole of ketone | Moles of reagent added per mole of ketone |
|---|---|---|
| Acetophenone | 0.025 | 1.025 |
| Aceto-*m*-xylene | .05 | 1.02 |
| Acetomesitylene | 1.03 | 0 |
| 5-Acetopseudocumene | 0.25 | 0.79 |
| Acetodurene | .97 | .04 |
| Acetoisodurene | .94 | .07 |
| Acetoprehnitene | .75 | .27 |
| Acetopentamethylbenzene | .93 | .01 |
| Diaceto-*m*-xylene | .16 | 1.82 |
| Diacetomesitylene | 1.82 | 0.26 |
| Diacetopseudocumene | 1.66 | .44 |
| Diacetodurene | 1.62 | .54 |
| Diacetoisodurene | 1.72 | .48 |
| Diacetoprehnitene | 1.68 | .46 |

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(1) Polymethylbenzenes. XVI. Paper XV, THIS JOURNAL, **58**, 1 (1936).

(2) Abstracted from a thesis by Cyrus Guss, submitted to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science, July, 1936.

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

(4) (a) Baum, *Ber.*, **28**, 3207 (1895); (b) Meyer, *ibid.*, **29**, 830 (1896); (c) Feith and Davies, *ibid.*, **24**, 3546 (1891); (d) Kohler and Baltzly, THIS JOURNAL, **54**, 4015 (1932).

(5) Klages and Lickroth, *Ber.*, **32**, 1549 (1899).

(6) Fuson and Walker, THIS JOURNAL, **52**, 3269 (1930).

(7) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927).

(8) Kohler and Thompson, *ibid.*, **55**, 3822 (1933).

(9) Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930).

enolization were obtained readily, but values for the amount of addition varied, often by as much as 5% especially for the diaceto compounds. At least three analyses of each ketone were made; the figures given are average values. Acetophenone is included in the table for comparison.

The results given in Table I show that all of the monoketones having methyl groups in both ortho positions to the carbonyl group are 100% enolized by methylmagnesium iodide. When only one ortho position is substituted by a methyl group the extent of enolization apparently is affected by the number of methyl groups elsewhere in the ring as shown by aceto-*m*-xylene, acetopseudocumene and acetoprehnitene which are enolized to the extent of 5, 24 and 75%, respectively. Among the diaceto compounds, enolization does not reach 100%, and diaceto-*m*-xylene is only 8% (per carbonyl group) enolized. Because of this result, it was thought that this compound might possibly be 4,6-diaceto-*m*-xylene, although the arguments of Meyer and Pavia[10] as well as those of Klages and Lickroth[5] (p. 1562) indicate quite strongly that the substance is 2,4-diaceto-*m*-xylene. Diacetomesitylene shows the greatest amount of enolization (90% per carbonyl group) of any of the diketones. The other five diketones are 80–85% enolized by the reagent; the degree of enolization is apparently affected but little, if any, by the relative positions of the two acetyl groups.

The authors are greatly indebted to Dr. A. F. Thompson, Jr., for suggestions and criticisms with reference to the Grignard analyses.

## Experimental Part[11]

The monoketones were prepared by the Friedel–Crafts synthesis from the hydrocarbons (1 mole), acetic anhydride (1.2 moles) and aluminum chloride (2.2 moles) in carbon bisulfide (400 cc.), according to the general procedure of Noller and Adams.[12] The products all distilled at nearly constant temperatures, except for small foreruns of hydrocarbons and some high boiling residues. The latter were worked up for diaceto compounds. The monoketones were all fractionated twice; in addition, acetodurene was crystallized from ether, and acetopentamethylbenzene from methyl alcohol.

For the diketones, the procedure was much the same, but using, per mole of hydrocarbon, 6 moles of aluminum chloride, 2.3 moles of acetic anhydride, and an amount of carbon disulfide sufficient to keep the reaction mixture fluid enough to stir well (200–500 cc.). The monoketones were removed from the products by fractionation and the residue was then distilled practically to dryness. The boiling points of the second fraction covered a wide range, but the distillate consisted almost entirely of the diketones which were crystallized from high boiling ligroin (A) or ether (B). Tables II and III show the physical constants and yields.

TABLE II

PREPARATION OF MONOKETONES

| Ketone | Hydrocarbon used, moles | Yield, g. | Yield, % | B. p., °C. | Mm. |
|---|---|---|---|---|---|
| 4-Aceto-*m*-xylene | 1.0 | 80 | 54 | 113 | 18[a] |
| Acetomesitylene | 0.5 | 43 | 72 | 121–123 | 18[b] |
| 5-Acetopseudocumene | 1.0 | 130 | 80 | 120–123 | 10[c] |
| Acetoisodurene | 1.0 | 143 | 81 | 135–137 | 16[d] |
| Acetoprehnitene | 0.5 | 58 | 70 | 122–124 | 8[e] |
| Acetodurene | 1.0 | 138 | 80 | 129–131 | 10[d] m. p., 73° |
| Acetopentamethylbenzene[f] | 1.0 | 153 | 80 | 144–145 | 8 m. p., 84° |

[a] Klages, *Ber.*, **35**, 2248 (1902). [b] Dittrich and Meyer, *Ann.*, **264**, 138 (1891). [c] Klages and Allendorf, *Ber.*, **31**, 1005 (1898). [d] Baum and Meyer, *ibid.*, **28**, 3213 (1895). [e] Claus and Föhlisch, *J. prakt. Chem.*, [2] **38**, 231 (1888). [f] New. *Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.11; H, 9.42. Found: C, 82.09; H, 9.21.

TABLE III

PREPARATION OF DIKETONES

| Ketone | Hydrocarbon used, moles | Monoketone, g. | Diketone, g. | M. p., °C. |
|---|---|---|---|---|
| 2,4-Diaceto-*m*-xylene | 1.0 | 70 | 41 | 109 A[a] |
| Diacetomesitylene | 1.0 | 70 | 38 | 44 A[b] |
| 3,5-Diacetopseudocumene[e] | 1.0 | 92 | 4.2 | 124 A |
| Diacetoisodurene | 1.0 | 94 | 14 | 121 A[c] |
| Diacetodurene | 0.5 | 15 | 11 | 178 B[c,d] |
| Diacetoprehnitene[f] | .5 | 35 | 8[g] | 113 B |

[a] Mayer and Pavia, *Ber.*, **29**, 2566 (1896). [b] Meyer, *ibid.*, **29**, 1413 (1896). [c] Baum and Meyer, *ibid.*, **28**, 3213 (1895). [d] Baum and Meyer, *ibid.*, **29**, 847 (1896). [e] New. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.85. Found: C, 77.24; H, 8.9. [f] New. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.07; H, 8.26. Found: C, 77.38; H, 8.50. [g] A white solid (3 g.) melting at 164–174° was formed as a by-product in this preparation. It was diacetyldurene (m. p. 178°); mixed m. p. 170–178°. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.07; H, 8.26. Found: C, 77.23, 77.08; H, 8.36, 8.12. This substance resulted from durene formed by action of aluminum chloride upon prehnitene during the prolonged, slow, diacetylation of prehnitene.

## Summary

1. Thirteen aceto- and diacetopolymethylbenzenes, three of them new compounds, have been analyzed in the Grignard machine with regard to enolization by methylmagnesium iodide.

2. All of the diortho substituted monoketones were 100% enolized by the reagent.

3. The degree of enolization of the mono ortho substituted monoketones was increased by the presence of methyl groups in the meta and para positions.

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(10) Meyer and Pavia, *Ber.*, **29**, 2566 (1896).

(11) Microanalyses by J. W. Opie.

(12) Noller and Adams, THIS JOURNAL, **46**, 1889 (1924).

4. The diketones were only 80–90% enolized by the reagent; the relative positions of the two acetyl groups had little effect on the degree of enolization.

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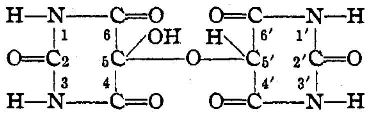
[CONTRIBUTION FROM KENT CHEMISTRY LABORATORY, UNIVERSITY OF CHICAGO]

# Studies in the Alloxantine Series[1]

BY DOROTHY NIGHTINGALE[2]

The formation and many of the reactions of alloxantine[3] can be explained by either the hemiacetal structure (I) of Piloty and of Slimmer and Stieglitz, or by the pinacol structure (II).



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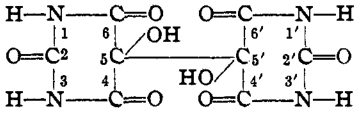

II

On the basis of the hemiacetal structure, it should be possible to prepare two isomeric methyl alloxantines and two unsymmetrical dimethyl alloxantines, namely, 1-methylalloxantine and 1′-methylalloxantine, and 1,3-dimethylalloxantine and 1′,3′-dimethylalloxantine. The first step, therefore, was to try to prepare the two possible monomethyl alloxantines, and then to determine by means of their hydrolytic products whether or not they maintained their identity. According to the pinacol formula they should be identical.

The 1-methylalloxantine can be prepared from methylalloxan and dialuric acid, and would be expected to yield these compounds on hydrolysis. Similarly, 1′-methylalloxantine should be formed by the union of alloxan and methyldialuric acid, and on hydrolysis should yield these same products. If the pinacol structure is correct, then either compound could yield a mixture of dialuric acid, methyldialuric acid, alloxan and methylalloxan. Tartar[4] concluded that the unsymmetrical dimethylalloxantines maintained their identity because the dimethyl murexides which he obtained from them gave dimethylalloxan and uramil, alloxan and dimethyluramil, respectively, when hydrolyzed with dilute hydrochloric acid. No further evidence was presented for their structures.

Alloxantine can be hydrolyzed with the following reagents and the hydrolytic products separated nearly quantitatively: (a) hydrochloric acid and the subsequent treatment of the solution with hydroxylamine hydrochloride, (b) hydroxylamine hydrochloride, (c) primary amines, (d) potassium acetate solution. When the mono or dimethyl alloxantines are used, however, this is no longer true. Solubilities are changed and yields lowered so that the hydrolytic products furnish little definite quantitative evidence as to probable structure.

Method (d) is useful for the isolation of only one hydrolytic product, namely, dialuric acid. According to Koech[5] freshly prepared potassium acetate solution hydrolyzes alloxantine to give alloxan and a quantitative yield of the slightly soluble potassium dialurate. The potassium salt of methyldialuric acid is very soluble in water, making this reaction of use only in detecting dialuric acid. A large excess of potassium acetate seems to be necessary for a quantitative yield of the potassium dialurate. With the theoretical amount, only a small quantity of potassium dialurate is precipitated. The reaction was applied to the methyl alloxantines with interesting results.

One rather unexpected result was observed, namely, the formation of potassium dialurate from 1′-methylalloxantine prepared from either 1-methyldialuric acid or its derivative 1-methyluramil. This result can be explained on the assumption that there is oxidation–reduction of methyldialuric acid by alloxan after hydrolysis.

According to Biilmann and Bentzon[6] alloxan-

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[1] Abstract of a portion of a dissertation presented by the author in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago in 1928. The investigation was carried out under the supervision of the late Professor Julius Stieglitz.

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[3] For a bibliography and brief discussion of the possible structures of alloxantine, see Davidson and Epstein, *J. Org. Chem.*, **1**, 305 (1936).

[4] H. V. Tartar, doctoral dissertation, University of Chicago, 1920.

[5] Koech, *Ann.*, **315**, 254 (1901).

[6] Biilmann and Bentzon, *Ber.*, **51**, 522 (1918).