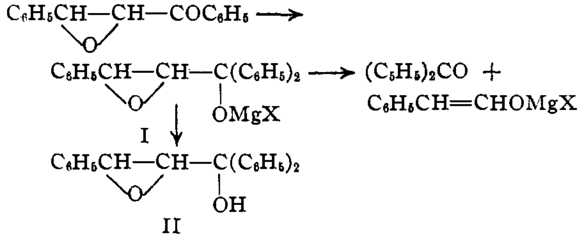
[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

The Action of Organometallic Compounds on Alpha Oxido Ketones

BY C. L. BICKEL

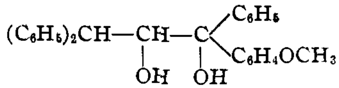
Alpha oxido ketones differing only slightly in structure behave quite differently when treated with phenylmagnesium bromide. Benzalacetophenone oxide reacts with one equivalent of phenylmagnesium bromide at −15°, giving the addition product I. Hydrolysis of this magnesium compound with acid gives the corresponding oxanol II. But at room temperature the magnesium compound I decomposes to give benzophenone and the magnesium derivative of the enolic form of phenyl acetaldehyde, a reaction represented below.



II

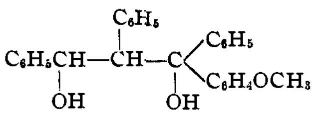
The oxide ring is not opened by phenylmagnesium bromide except through cleavage.[1] *o*-Chlorobenzalacetophenone oxide behaves in an analogous manner, opening of the oxide ring taking place only by cleavage of the magnesium derivative of the carbinol at higher temperatures.[2] Both of the above oxido compounds give a similar reaction with lithium phenyl, except that the lithium derivative of the carbinol decomposes more slowly.[2]

Conversely, Bergmann[3] found that benzal-*p*-methoxyacetophenone oxide behaves quite differently with phenylmagnesium bromide. His results indicated that two equivalents of reagent add to the oxide at room temperature with no resultant cleavage. Bergmann did not determine the structure of this product, but offered two possible structures, III and IV.



$(C_6H_5)_2CH-CH(OH)-C(OH)(C_6H_5)C_6H_4OCH_3$

III



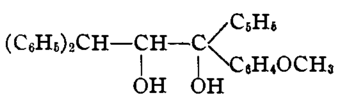
$C_6H_5CH(OH)-CH(C_6H_5)-C(OH)(C_6H_5)C_6H_4OCH_3$

IV

Either of these compounds would be formed by fission of the oxide ring and attendant addition. The point at which the ring opens would determine the nature of the product.

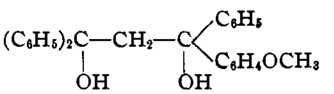
The present paper is concerned with the reaction of benzal-*p*-methoxyacetophenone oxide with lithium phenyl, a more detailed study of the reaction with phenylmagnesium bromide and the determination of the structure of the product first obtained by Bergmann.

Chromic acid oxidation of the compound obtained by Bergmann gave benzophenone and *p*-methoxybenzophenone as products. Only two compounds, III and VI, which could have been formed in the Grignard reaction would give these two oxidation products.



$(C_6H_5)_2CH-CH(OH)-C(OH)(C_6H_5)C_6H_4OCH_3$

III



$(C_6H_5)_2C(OH)-CH_2-C(OH)(C_6H_5)C_6H_4OCH_3$

VI

Compound VI would be formed by rearrangement of the oxide to give a ketone which would add phenylmagnesium bromide. Compound III would be formed by the opening of the oxide ring by phenylmagnesium bromide with attendant addition.

The tertiary carbinol VI was synthesized from the beta diketone VII, the first reaction with phenylmagnesium bromide giving the two isomeric compounds VIIA and VIIB. The treatment of each of these isomers with lithium phenyl gave the carbinol VI, whose structure was confirmed by oxidation to benzophenone and *p*-methoxybenzophenone. The synthesis is represented by the accompanying formulas.

The carbinol VI was not identical with the product obtained from the *p*-methoxy oxide. Therefore, by elimination, the structure of the product obtained by Bergmann is represented by formula III.

A most interesting result was obtained when benzal-*p*-methoxyacetophenone oxide was treated with lithium phenyl in ether solution. None of

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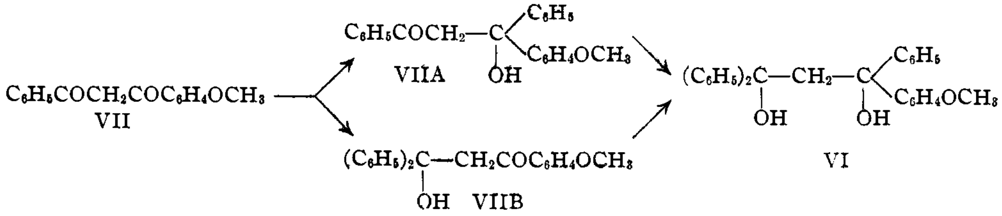
(1) Kohler, Richtmyer and Hester, THIS JOURNAL, **53**, 205 (1931).

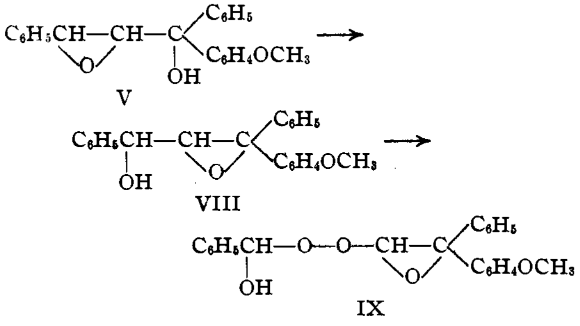
(2) Kohler and Bickel, *ibid.*, **57**, 1099 (1935).

(3) Bergmann and Wolff, *ibid.*, **54**, 1644 (1932).



the compound III could be obtained. Instead, the oxide gave results analogous to those obtained with benzalacetophenone oxide or the corresponding *o*-chloro compound. In cold solution the oxanol V was the only product; at room temperature the expected cleavage of the oxanol V took place. The glycol III was produced in good yield when the oxanol V was treated with excess phenylmagnesium bromide.

The oxanol V behaves like the corresponding unsubstituted oxanol II when treated with a dilute alcoholic solution of sodium hydroxide. An isomeric oxanol VIII is produced. This oxanol is apparently much more unstable than the other known compounds of similar structure, cleavage and autoxidation proceeding very rapidly in the laboratory air. Indeed it is difficult to obtain a pure sample and it is more difficult to keep a pure sample long enough to determine its percentage composition, crystal form and melting point with any great degree of accuracy. Cleavage and autoxidation of this oxanol give a peroxide IX which forms benzoic acid and *p*-methoxybenzophenone by chromic acid oxidation.



Bergmann treated the oxide with excess of phenylmagnesium bromide at room temperature. One equivalent of phenylmagnesium bromide added inversely to a cold solution of the oxide should provide the best conditions for the production of the oxanol V. Yet when these conditions were fulfilled, 50% of the oxide was recovered unchanged and the remaining 50% was converted into the product obtained by Bergmann.

The inactivity of the oxide ring of the *p*-methoxy compound toward lithium phenyl suggests the possibility that oxide rings in general are unattacked by lithium phenyl under conditions which would give a reaction with phenylmagnesium bromide. Experiments now in progress will attempt to settle this question.

An explanation of the difference in the reaction of benzalacetophenone oxide and benzal-*p*-methoxyacetophenone oxide with phenylmagnesium bromide is as yet not evident. At least two explanations can be offered from the facts at hand. The anisyl group may activate the oxide ring so that fission of the oxide ring is made much easier. This would permit simultaneous addition to the carbonyl group and to the oxide ring, producing a magnesium derivative having no tendency to break up. The alternative is that the anisyl group strengthens the C–C bond between the carbonyl group and the oxide ring, thus preventing the cleavage of the primary magnesium derivative.

The fact that the anisyl compound shows addition to the oxide ring at low temperatures—while the unsubstituted oxide does not—indicates that the first explanation is more probably correct. Research now in progress may provide a more adequate explanation for this difference in behavior.

Experimental Part

2-Hydroxy-1,3,3-triphenyl-1-anisyl Propanol, III

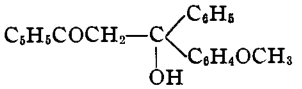
Inverse Grignard.—One equivalent of phenylmagnesium bromide in ether was added slowly to a stirred solution of 15 g. of benzal-*p*-methoxyacetophenone oxide in 300 cc. of ether maintained at −15°. The cold solution was stirred for thirty minutes after complete addition of the reagent and was then decomposed immediately with iced acid. The ether yielded 12 g. of the 132° compound III described by Bergmann, in addition to 4 g. of unchanged oxide. About 3.5 g. of unchanged oxide was also reclaimed from the solid clinging to the walls of the reaction flask.

Excess Grignard.—To a stirred solution of four equivalents of phenylmagnesium bromide in ether was added 15 g. of solid benzal-*p*-methoxyacetophenone oxide. After boiling the stirred solution for one hour the product was isolated in the usual way. The yield was 23.5 g. of the 132° compound III, compared with a calculated yield of 24.2 g.

Oxidation.—Chromic acid oxidation of the carbinol III in glacial acetic acid solution gave benzophenone and *p*-methoxybenzophenone, identified by means of known samples. No benzoic acid could be detected.

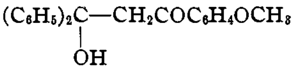
3-Hydroxy-1,3,3-triphenyl-1-anisyl Propanol, VI.—To a stirred solution of four equivalents of phenylmagnesium bromide in ether was added in the course of two hours 25 g. of *p*-methoxydibenzoylmethane suspended in ether. After the mixture had been stirred and refluxed for four hours, hydrolysis with iced acid was accomplished as usual. The product was fractionally crystallized from methyl alcohol (kept slightly acid with glacial acetic acid to prevent cleavage), giving about 7 g. each of two isomeric compounds.

The 132° isomer VIIA is much more insoluble in methyl alcohol and crystallizes in small needles. Oxidation by chromic acid in glacial acetic acid solution gave benzoic acid and *p*-methoxybenzophenone. The 132° isomer is therefore



$$\mathrm{C_6H_5COCH_2{-}}\underset{\underset{\textstyle \mathrm{OH}}{|}}{\mathrm{C}}\begin{matrix}\diagup \mathrm{C_6H_5}\\ \diagdown \mathrm{C_6H_4OCH_3}\end{matrix}$$

The 118° isomer VIIB is quite soluble in methyl alcohol and crystallizes in small needles. Oxidation by chromic acid gave anisic acid and benzophenone. The 118° isomer is therefore



$$(\mathrm{C_6H_5})_2\underset{\underset{\textstyle \mathrm{OH}}{|}}{\mathrm{C}}{-}\mathrm{CH_2COC_6H_4OCH_3}$$

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.48; H, 6.07. Found: (132°) C, 79.36; H, 6.17; (118°) C, 79.31; H, 6.20.

Lithium Phenyl and the (118°, 132°) Isomer.—To a stirred solution of four equivalents of lithium phenyl in ether cooled to 0° was added 3 g. of the 132° isomer suspended in a small volume of ether. After two hours of stirring at 0° the solution was hydrolyzed in the usual way with iced acid. The dried ethereal solution, diluted with petroleum ether, deposited clusters of stout needles melting at 150°. The yield was about 3 g. The carbinol is fairly soluble in ether, quite soluble in methyl alcohol and insoluble in petroleum ether. The 118° isomer gave the same 150° carbinol in a similar reaction.

Anal. Calcd. for $C_{28}H_{26}O_3$: C, 81.91; H, 6.39. Found: C, 81.86; H, 6.37.

Oxidation.—Chromic acid oxidation of the carbinol VI gave benzophenone and *p*-methoxybenzophenone, identified by means of known samples.

2-Oxido-1,3-diphenyl-1-anisyl Propanol, V.—To a stirred solution of one equivalent of lithium phenyl in 200 cc. of ether maintained at −15° was added 10 g. of solid benzal-*p*-methoxyacetophenone oxide over a period of thirty minutes. Forty-five minutes of additional stirring at −15° produced a precipitate. Decomposition of this reaction mixture with iced acid gave an ether solution which deposited large plates melting at 136°. The yield was 12 g. None of the carbinol III could be detected. The oxanol V is quite soluble in acetone, moderately soluble in ether, insoluble in petroleum ether and forms beautiful plates from an acetone–petroleum ether mixture.

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.48; H, 6.07. Found: C, 79.36; H, 6.12.

Oxidation.—Chromic acid oxidation of the oxanol V gave benzoic acid and *p*-methoxybenzophenone, identified by means of known samples.

Addition of Phenylmagnesium Bromide.—Two grams of solid V was added to a stirred solution of three equivalents of phenylmagnesium bromide in ether. After being boiled for one and one-half hours the solution was treated with iced acid and the product isolated in the usual way. The ether gave 2.5 g. of the 132° compound III, identified by a mixed melting point with known material.

Cleavage with Lithium Phenyl.—A stirred ether solution of three equivalents of lithium phenyl to which 5 g. of the solid V had been added was boiled for three hours. After decomposition with iced acid, the only solid product which could be isolated was *p*-methoxytriphenylcarbinol, identified by means of a known sample. The remaining material was the usual resinous aldehyde.

Rearrangement with Bases: 2-Oxido-1,3-diphenyl-3-anisyl Propanol, VIII.—To a solution of 0.2 g. of potassium hydroxide in 100 cc. of methyl alcohol was added 5 g. of the sparingly soluble oxanol V. The mixture was allowed to stand for three days during which time the solid gradually dissolved, then poured into ice water. The product crystallized from ether–petroleum ether in stout plates melting at about 120°. The melting point of the pure substance was not determined exactly because of very rapid deterioration in laboratory air. The rearrangement product is very soluble in methyl alcohol, acetone and ether and is but sparingly soluble in petroleum ether. No other product was isolated except the peroxide formed by autoxidation of VIII. The rapid decomposition of the compound made an accurate analysis most difficult.

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.48; H, 6.07. Found: C, 79.1; H, 5.9.

Oxidation.—Chromic acid oxidation of the oxanol VIII gave only benzoic acid and *p*-methoxybenzophenone as products.

Autoxidation: The Peroxide, IX.—The oxanol VIII is autoxidized very rapidly in the air of the laboratory. A freshly prepared sample oiled and developed the odor of benzaldehyde after a few minutes of exposure. Complete autoxidation gave a white powder which was recrystallized from ether–petroleum ether. It separates as fine white needles and melts with brisk bubbling at 150°. It is sparingly soluble in acetone, methyl alcohol and ether and insoluble in petroleum ether.

Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72.48; H, 5.54. Found: C, 72.4; H, 5.7.

Oxidation.—Chromic acid oxidation of the peroxide IX gave benzoic acid and *p*-methoxybenzophenone as products.

2-Oxido-1,1,3-triphenyl Propanol.[4]—Ten grams of solid benzalacetophenone oxide was added to a stirred solution of two equivalents of lithium phenyl in ether maintained at −15°. After forty-five minutes of stirring at −15° the solution was decomposed with iced acid. The ether gave a good yield of the 130° oxanol previously obtained by the use of phenylmagnesium bromide. The identity of the compound was verified by a mixed melting point with known material.

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(4) Kohler, Richtmyer and Hester, THIS JOURNAL, **53**, 214 (1931).

2-Oxido-1,1-diphenyl-3-(*o*-chlorophenyl) Propanol.[5]— Ten grams of solid *o*-chlorobenzalacetophenone oxide was added to a stirred ethereal solution of two equivalents of lithium phenyl maintained at −15°. After forty-five minutes of stirring at −15°, the solution was decomposed with iced acid. The ether gave a good yield of the 107–108° oxanol previously obtained by the use of phenylmagnesium bromide. The oxanol was identified by comparison with a known sample.

The author gratefully acknowledges a gift from the Milton Fund of Harvard University, with which the starting materials used in this problem were purchased.

Summary

The action of lithium phenyl and of phenylmagnesium bromide on alpha oxido ketones is compared. The structure of the compound formed by the reaction of phenylmagnesium bromide and benzal-*p*-methoxyacetophenone oxide has been determined.

EXETER, N. H. RECEIVED DECEMBER 16, 1936

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[5] Kohler and Bickel, THIS JOURNAL, **57**, 1100 (1935).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA AND MILLS COLLEGE]

Stereochemistry of Deuterium Compounds. I. Optical Rotation of Methylhexyldeuterocarbinol

BY LEONA YOUNG AND C. W. PORTER

Many unsuccessful attempts have been made to obtain optically active compounds in which asymmetry is dependent upon differences between hydrogen and deuterium. It was our aim, a year ago, to prepare stereoisomeric compounds of the type RR′CHD and to isolate the *d* and *l* forms of these compounds. Attempts to prepare such compounds from optically active halides, through the Grignard reaction, led to complete racemization.[1] Attempts to isolate an optically active hydrocinnamic acid from the products formed when cinnamic acid was reduced by deuterium failed, presumably, on account of slight differences in the solubilities of the alkaloid salts. Failure to resolve racemic phenyldeuteroacetic acid, C_6H_5-CHD-COOH, into active components through fractional crystallization of alkaloid salts was attributed to the same cause.[2]

Biilman, Jensen and Knuth claim to have produced a measurable optical rotation in camphane through the substitution of deuterium for hydrogen in a methylene group[3] but their findings have not been confirmed and their technique has been the subject of adverse criticism.[4]

Recently we turned our attention to a comparison of the rotations of compounds in which the hydrogen and deuterium are not attached directly to the asymmetric carbon atom. One example of this type has been reported.[5] Methyl hexylcarbinol was resolved into active components and the dextrorotatory fraction was used in the experiments reported here. The active alcohol was esterified by treatment with acetyl chloride and the ester was, in turn, hydrolyzed with deuterium oxide. The rotation of the recovered alcohol was lower than that of the original sample. This alcohol was then reconverted into the original form through esterification and subsequent hydrolysis with ordinary water. The recovered compound had the same rotation as that of the original sample. The experiment was repeated several times and, within the limits of experimental error, the results were the same.

The measured rotations were as follows:[6]

	I	II	III
Original carbinol	17.45	19.00	17.90
Deuterium derivative	17.20	18.70	17.60

The average difference in rotations of the two compounds was 0.28 scale divisions or 0.11°. We feel justified, therefore, in reporting a real difference between the optical properties of ordinary methylphenylcarbinol and the compound formed

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[1] Porter, THIS JOURNAL, **57**, 1436 (1935).

[2] Schultz and Porter, unpublished work, 1935.

[3] Biilman, Jensen and Knuth, *Ber.*, **69**, 1031 (1936).

[4] Leffler and Adams, THIS JOURNAL, **58**, 1555 (1936).

[5] Clemo and McQuillen, *J. Chem. Soc.*, 808 (1936).

[6] The measurements were made with a Fric polarimeter. The scale divisions on this instrument are equivalent to 0.404 degrees. The reading +19.00 corresponds to 7.68°. The specific rotation of the pure dextro compound with green light (5461 Å.) is +11.80°. Our resolution of the racemic mixture was not quantitative but for the purpose of this study it was not necessary to have complete separation. It was necessary only to have a preparation of known rotatory power and to be sure that no racemization occurred in the treatment to which the compound was subjected.