[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Reaction between Cyclic β-Diketones and Grignard Reagents. 1,3-Diketo-2,2-dimethylhydrindene[1]

BY T. A. GEISSMAN AND VSEVOLOD TULAGIN

The work of Kohler and his students[2] has established the factors governing the type of reaction which will occur when straight-chain β-diketones and α-oxidoketones are treated with alkyl- and arylmagnesium halides and has shown that in certain cases cleavage of the diketone or of the oxidoketone occurs. While no mechanism has been established for the reaction it has been pointed out by Kohler[2a] that in the case of the α-oxidoketone the cleavage proceeds in a manner that bears a formal resemblance to the reversal of the aldol condensation. It is evident that the cleavage of β-diketones can be similarly compared to the reversal of the aldol condensation, as well as to their cleavage by alkali.[3]

Among the factors which may play an important part in the cleavage reaction is the spatial disposition of the groups concerned and the study of the reaction of cyclic β-diketone with a Grignard reagent would give information which should be valuable in seeking a mechanism for the cleavage. Only two examples of this type of reaction have so far been described, Wedekind and Miller[4] having reported the normal addition of two moles of ethylmagnesium bromide to 2,2,4,4-tetramethylcyclobutanedione-1,3 and Weiss and Luft[5] having studied the reaction of 1,3-diketo-2,2-dimethylhydrindene with phenylmagnesium bromide. Weiss and Luft succeeded in isolating in poor yield only one compound, derived from the addition of one mole of the reagent to the diketone, and while they recognized the possibility of cleavage of the diketone they failed to demonstrate clearly, either by an unequivocal structure proof of the single product obtained or by a search for other products of the reaction, that cleavage had not occurred.

In view of this paucity of information concerning reactions involving cyclic β-diketones the reaction of phenylmagnesium bromide with 1,3-diketo-2,2-dimethylhydrindene has been studied in detail in an attempt to determine whether cleavage does or can be induced to occur, and the structures of the products obtained have been proved by their relationship to compounds of known structure.

The treatment of 1,3-diketo-2,2-dimethylhydrindene with one mole of phenylmagnesium bromide in ether under the conditions used by Weiss and Luft gave a mixture which yielded two compounds in approximately equal amounts, one a mono-addition product (I), which was the product isolated by the earlier investigators, and the other a diaddition compound (II). The monoaddition product (I) could be obtained in good yield as the main product of the reaction when phenylmagnesium bromide was added to a large excess (nearly 4 moles) of the diketone, and the diaddition product (II) was formed in good yield when the diketone was allowed to react with an excess of the reagent. The monoaddition compound (I) was oxidized to *o*-benzoylbenzoic acid. It could be converted into a methyl ether (III) and an ethyl ether (IV), the former of these having been obtained by the earlier workers. Treatment of the methyl ether with phenylmagnesium bromide yielded the monomethyl ether (V) of the diaddition compound (II).

The reaction of the monoaddition compound (I) with a second mole of phenylmagnesium bromide would, if cleavage occurred, be expected to lead to the compound formulated as IIa; if addition of the second mole of reagent followed the normal course at the remaining carbonyl group, compound II would be formed. A choice between these possibilities can easily be made since IIa on oxidation would yield *o*-benzoylbenzoic acid while II would yield *o*-dibenzoylbenzene. The oxidation of the compound obtained yielded *o*-dibenzoylbenzene and its structure is therefore represented by II. The other properties shown by the diaddition product lead to the same conclusion. It can be converted into a dichloro derivative (VI) by the action of dry hydrogen chloride in benzene solution. Treatment of II and of its monomethyl ether (V, derived from I)

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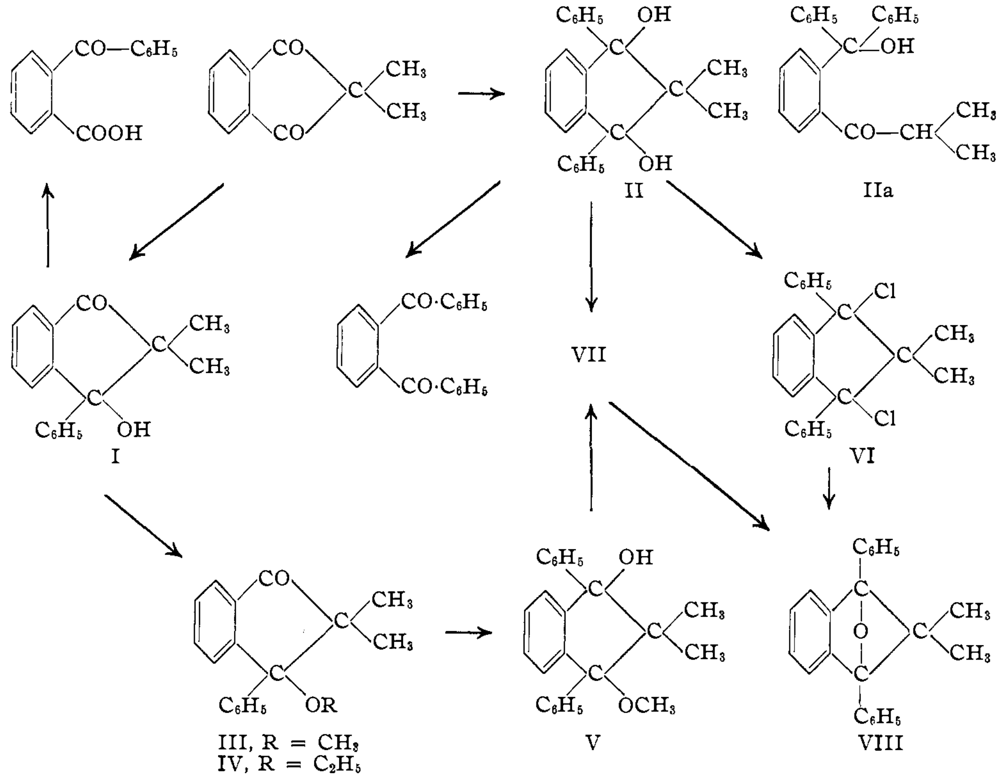
[1] Presented before the 1941 Meeting of the American Association for the Advancement of Science, Pasadena, California, June 16–21 (1941).

[2] (a) Kohler, Richtmyer and Hester, THIS JOURNAL, **53**, 205 (1931); (b) Kohler and Erickson, *ibid.*, **53**, 2301 (1931).

[3] Bradley and Robinson, *J. Chem. Soc.*, 2356 (1926).

[4] Wedekind and Miller, *Ber.*, **44**, 3285 (1911).

[5] Weiss and Luft, *Monatsh.*, **48**, 337 (1927).

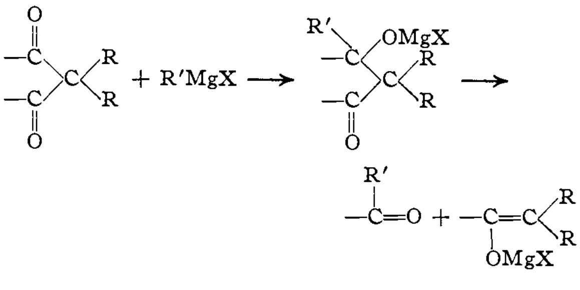


with hydrogen chloride in methanol yielded a substance (VII) which contained no methoxyl but for which satisfactory analyses could not be obtained. When VII was boiled with methanol a compound was obtained which contained neither methoxyl or halogen and whose composition is in agreement with its formulation as the oxido compound VIII. This compound (VIII) was formed in an analogous way from the dichloro compound (VI).

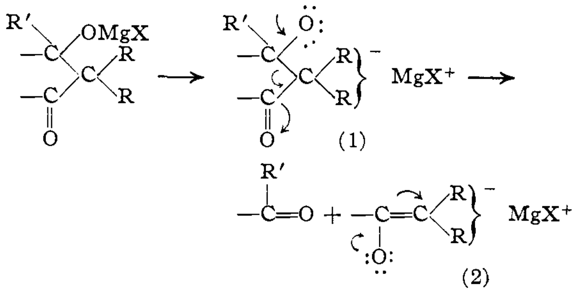
Since under the conditions of the reactions so far mentioned, leading to the compounds I and II, no evidence of cleavage of the diketone was obtained, attempts were made to bring about cleavage. Treatment of the mono-addition compound (I) with an equivalent amount of phenylmagnesium bromide and heating the resulting mixture at the boiling point of isopropyl ether for an extended period, or heating a solution produced by the addition of the reagent to an excess of the diketone for an extended period at the boiling point of benzene gave results in terms of products isolated which were equivalent to those obtained in carrying out the reaction under mild conditions. In no case was evidence obtained of any reaction other than the normal ones so far described.

While the absence of cleavage in the addition of excess phenylmagnesium bromide to the diketone could be attributed to an addition to the second carbonyl group faster than a cleavage of the product of addition to the first carbonyl group, the experiments designed to favor the cleavage reaction if it were possible indicate that cleavage does not occur even when the addition of a second mole of reagent does not take place.

Discussion.—The formulation of the cleavage of a β-diketone by an organomagnesium halide in the following way



is non-committal and gives no explanation of the mechanism of the change. A strict analogy with the reversal of the aldol condensation, such as was suggested by Kohler, would lead to (A)

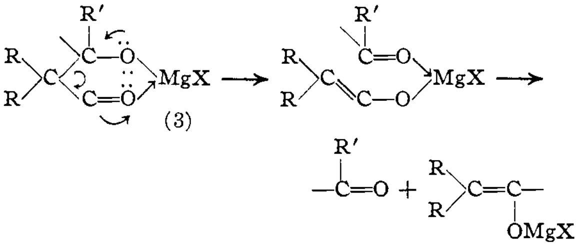


(1)

(2)

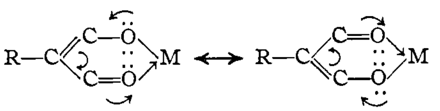
While there is no evidence that halomagnesium alcoholates such as (1) are ionic in nature as indicated, the properties of halomagnesium enolates such as (2) are in harmony with their formulation as the resonance forms shown, since it has been amply demonstrated[6] that such enolates can react either at the oxygen or the carbon atom bearing the resonating charge.

A modification of this picture which is in better agreement with certain modern concepts of the nature of organic halomagnesium derivatives[7] is the following (B)

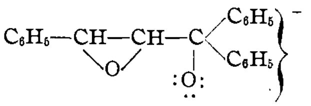


(3)

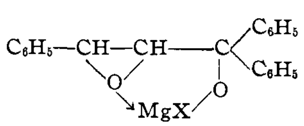
The product (3) resulting from the addition of a mole of Grignard reagent to the β-diketone resembles, as written, the chelated enolate of an enolizable β-diketone and the cleavage reaction involves a bond shift which closely resembles the interconversion of the resonance forms of such enolates



These considerations indicate the importance of taking into account the steric configurations of the groups involved and it is with this matter that the present study deals. In the case of 1,3-diketo-2,2-dimethylhydrindene a chelated complex such as (3) could not form and, if such a complex were a necessary step in the cleavage reaction, cleavage would not occur. The fact that no cleavage was observed is strong support for the postulation of such an intermediate. Further evidence may be found in the observation of Kohler[2a] that while 1,1,3-triphenyl-2,3-oxidopropanol-1 is rapidly cleaved by phenylmagnesium bromide, strong alkali does not cleave it but rearranges it to the isomeric 1,1,3-triphenyl-1,2-oxidopropanol-3. In this case, therefore, the formation of the ion

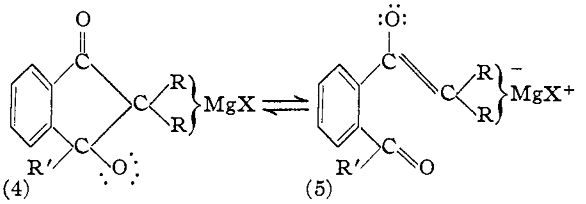


is not sufficient to bring about cleavage, but when a complex such as



can form, cleavage ensues.

It is clear that the evidence adduced does not constitute proof that the chelated intermediate precedes cleavage since if cleavage proceeded by another course (for example, A) the spatial distribution of the groups in a cyclic β-diketone might favor the maintenance of the cyclic member of the equilibrium



(4) (5)

Evidence as to the behavior of the compound whose halomagnesium derivative is represented as (5) toward alkali and Grignard reagents is necessary to enable a decision to be reached on this point.

Experimental

1,3-Diketo-2,2-dimethylhydrindene.—This was prepared by the methylation of the sodium salt of the monomethyl compound formed by the condensation of ethyl propionate and ethyl phthalate, according to Wislicenus and Kotzle.[8]

The Reaction of 1,3-Diketo-2,2-dimethylhydrindene with Phenylmagnesium Bromide. 1. Equimolar Amounts.—To 4 g. of the diketone in ether solution was added one equivalent of phenylmagnesium bromide. The reaction was vigorous and accompanied by the evolution of heat. After two hours the reaction mixture was decomposed with iced ammonium chloride solution, the ether layer separated and evaporated and the residual oil subjected to

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[6] Kohler and Peterson, THIS JOURNAL, **55**, 1073 (1933); Cope, *ibid.*, **56**, 721 (1934); Fuson, Fugate and Fisher, *ibid.*, **61**, 2362 (1939).

[7] J. R. Johnson in Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 1650–1651.

[8] Wislicenus and Kotzle, *Ann.*, **252**, 82 (1889); see also Koelsch and Byers, THIS JOURNAL, **62**, 560 (1940).

steam distillation. Along with diphenyl a small amount of the diketone was present in the distillate. The tar left in the distilling flask was taken up in ether and, after drying over sodium sulfate, the ether was removed and the residue dissolved in ligroin (b. p. 75–105°). On cooling an oil separated and upon standing overnight it became crystalline. The supernatant liquid was decanted and, upon scratching, deposited a second crop of white crystals. These fractions were recrystallized separately. The first (oiled-out) fraction formed thick colorless needles from ligroin, m. p. 141–142°. This is the monoaddition product, 1-phenyl-2,2-dimethyl-3-ketohydrindenol-1 (I).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39; mol. wt., 252. Found: C, 80.65; H, 6.25; mol. wt. (Rast), 256.

The second fraction formed colorless needles from ligroin, m. p. 141–142°. This is the diaddition product, 1,3-diphenyl-2,2-dimethylhydrindenediol-1,3 (II). A mixture of I and II melted at 115–125°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71; mol. wt., 330. Found: C, 83.37; H, 6.85; mol. wt. (Rast), 342.

2. **Using Excess Diketone. Preparation** of I.—Twenty grams (0.11 mole) of 1,3-diketo-2,2-dimethylhydrindene was dissolved in anhydrous benzene containing a little ether. To this solution was added dropwise a solution containing 0.03 mole (by titration) of phenylmagnesium bromide. The reaction mixture was cooled during the addition of the reagent, which required between two and three hours. The reaction mixture was allowed to stand overnight and then decomposed with iced hydrochloric acid. The benzene–ether layer was washed with sodium bicarbonate solution and water and the solvents removed by distillation. The residual oil was steam-distilled under reduced pressure, about 13 g. of the diketone being recovered from the distillate. After all of the excess diketone had been removed the residue in the distilling flask crystallized spontaneously. Recrystallized from ligroin it weighed 5.7 g. (75%, based on the amount of phenylmagnesium bromide used) and melted at 141–142°. It was the monoaddition product (I) as shown by a mixed melting point determination.

When ether alone was used as the reaction solvent a precipitate was formed upon addition of the Grignard reagent. This is evidently a complex formed of the diketone and the reagent since larger amounts of starting material are recovered and a lower yield of product is obtained on working up the reaction mixture in the manner described above.

3. **Excess Phenylmagnesium Bromide. Preparation of II.**—To a solution of 4 g. of the diketone in 75 ml. of anhydrous benzene was added an excess (3 moles) of phenylmagnesium bromide over about fifteen minutes. The color of the reaction mixture became yellow after one mole of the reagent had been added, turning to an orange-red upon the addition of the second mole. Addition of the remainder of the reagent caused no further change to take place. Upon standing for three hours the color of the solution faded to an orange yellow. The reaction mixture was decomposed with iced hydrochloric acid and the solvents and diphenyl removed by steam distillation. The residue in the distilling flask crystallized during the steam distillation. It was removed and recrystallized from ligroin. There was obtained 6.5 g. (86%), m. p. 141–142°. A mixed melting point showed it to be II.

Oxidation of I.—Oxidation of I in acetic acid solution with potassium dichromate yielded *o*-benzoylbenzoic acid, identified by its melting point and mixed melting point with an authentic sample; neutral equivalent calculated, 226; found, 228.

Oxidation of II.—A mixture of 1.6 g. of II, 15 ml. of concentrated nitric acid and 60 ml. of water was refluxed for one and one-half hours. A yellow oil formed and was removed and washed with sodium bicarbonate solution. Crystallized from a mixture of benzene and ligroin, it melted at 143–144°. Treatment of this material for a short time with sodium dichromate–acetic acid followed by recrystallization raised its m. p. to 148°; reported[9] for *o*-dibenzoylbenzene, 148°. It formed a phenylhydrazone, m. p. 165–167°; reported,[10] 165°.

1-Phenyl-1-methoxy-3-keto-2,2-dimethylhydrindene (III).—A methanol solution of 2 g. of I was saturated with dry hydrogen chloride. The solution was concentrated by distillation and upon cooling there was obtained 1.8 g. of a colorless crystalline compound, m. p. 160–162°; reported,[3] 160–162°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81; OCH_3, 11.66. Found: C, 81.42; H, 6.54; OCH_3, 11.78.

1-Phenyl-1-ethoxy-3-keto-2,2-dimethylhydrindene (IV).—Prepared essentially as described for the methyl ether but using ethanol instead of methanol, this compound was obtained as colorless needles, m. p. 135–136°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.76; H, 7.02. Found: C, 81.54; H, 6.81.

1,3-Diphenyl-1-methoxy-2,2-dimethylhydrindenol-3 (V).—A solution of 0.9 g. of the methyl ether III in benzene was treated with an amount of phenylmagnesium bromide somewhat in excess of that required. After three hours at room temperature the reaction mixture was decomposed, the benzene layer separated, dried and evaporated. The residue crystallized from ligroin in colorless needles, m. p. 171.0–171.3°; reported,[3] 172–174°.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.67; H, 7.02; OCH_3, 9.08. Found: C, 83.92; H, 6.51; OCH_3, 9.11.

1,3-Diphenyl-1,3-endoxo-2,2-dimethylhydrindene (VIII).—When either the monomethyl ether (V) of II or II itself was treated with dry hydrogen chloride a crystalline compound separated from the solution. It melted with extensive decomposition and gas evolution at 172–174°. No consistent analyses could be obtained for this substance (VII), probably because of its instability and partial decomposition when it was dried for analysis. It contained chlorine but not methoxyl. When a solution of this substance in methanol was boiled until hydrogen chloride was no longer present in the vapors and the solution evaporated, a substance remained which crystallized from ether–petroleum ether. Recrystallized from ligroin, methanol and again from ligroin it melted at 70°. A Zeisel determination showed that it contained no methoxyl group. It was halogen-free.

Anal. Calcd. for $C_{23}H_{20}O$: C, 88.42; H, 6.45. Found: C, 88.37; H, 6.39.

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[9] Kohler, THIS JOURNAL, **40**, 231 (1918).

[10] Guyot and Catel, *Bull. soc. chim.*, [3] **35**, 1138 (1906).

1,3-Diphenyl-1,3-dichloro-2,2-dimethylhydrindene (VI).—A solution of 1 g. of the diaddition compound II in anhydrous benzene was saturated with dry hydrogen chloride. A few grains of anhydrous calcium chloride were present to remove water formed in the reaction. After removal of the benzene the product was crystallized from ligroin. It melted at 177–178°.

Anal. Calcd. for $C_{23}H_{20}Cl_2$: C, 75.20; H, 5.49; Cl, 19.31. Found: C, 75.09; H, 5.32; Cl, 19.33.

Treatment of this compound with boiling methanol converted into the oxido compound VIII, m. p. 70°.

Attempts to Cleave the Monoaddition Compounds I.—1. To a solution of 8 g. of 1,3-diketo-2,2-dimethylhydrindene in anhydrous benzene was added over three hours an ether solution of 0.025 mole of phenylmagnesium bromide. The ether was removed by distillation until the boiling point of the solution reached 80°. The solution was refluxed for sixteen hours. At the end of this time an excess of phenylmagnesium bromide was added and the diaddition product isolated as described above. There was obtained a 79% yield of II. While this does not represent a quantitative recovery, the isolation of pure material from the last residues of the product in crystallization mother liquors was difficult. No evidence for the presence of any other compound could be obtained.

2. To a solution of 2.60 g. of the monoaddition compound (I) in 100 ml. of anhydrous isopropyl ether was added a carefully measured amount of phenylmagnesium bromide in ether corresponding to exactly one mole of reagent. A white precipitate formed during addition of the reagent. The ethyl ether was removed and the solution refluxed at the boiling point of isopropyl ether for sixteen hours. Upon working up the reaction mixture the starting material was recovered unchanged. No other product could be found. The yield of recovered product was, after recrystallization, only about 70% but this corresponds to experience in isolating and purifying the substance in other experiments. The formation of a small amount of the diaddition compound (II) during the addition of the reagent to the monoaddition compound could easily account for the poor recovery, since the presence of an amount of the diaddition compound too small for isolation would undoubtedly, in view of its similarity in solubility and crystallizing tendency, make it difficult to induce all of the other substance to crystallize. For example, Weiss and Luft[5] were able to obtain only a 20% yield of I from what has been shown in this work to be a mixture of I and II.

Summary

1. The reaction of 1,3-diketo-2,2-dimethylhydrindene with phenylmagnesium bromide has been studied and it has been found that normal addition of either one or two moles of the reagent to the carbonyl groups of the diketone occurs. No evidence for cleavage was obtained.

2. The results have been discussed in their relation to the reaction of straight-chain β-diketones with Grignard reagents, where cleavage of the molecule can be brought about.

LOS ANGELES, CALIFORNIA RECEIVED JULY 28, 1941

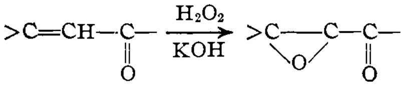
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Osage Orange Pigments. VIII.[1] Oxidation

BY M. L. WOLFROM AND A. S. GREGORY

In a previous communication[2] from this Laboratory, it was shown that osajin dimethyl ether yielded anisic (*p*-methoxybenzoic) acid on oxidation with alkaline hydrogen peroxide and that pomiferin trimethyl ether yielded veratric (3,4-dimethoxybenzoic) acid under the same conditions. It is now shown that the oxidation of pomiferin trimethyl ether (I) proceeds through the intermediate formation of a ketoxide (II), isolatable in high yield, and designated pomiferin trimethyl ether 2,3-epoxide. Such an intermediate was not isolatable in the oxidation of osajin dimethyl ether, but there is no reason to believe that the reaction does not follow a similar course. A ketoxide of iso-osajin was obtained. The expected entity III apparently underwent extensive destruction under the oxidizing conditions and was not isolated.

Weitz[3] found that α,β-unsaturated ketones reacted with hydrogen peroxide in the presence of low alkalinity to form compounds designated ketoxides which differed from the initial ketone by the addition of one atom of oxygen to the molecule and liberated iodine in the hot, but not in the cold, from an acetic acid solution of potassium iodide. The structures of these substances were established definitely.[4] Such ketoxides were not isolatable in all cases, further oxidation being at times more rapid than their formation.



$$>\mathrm{C}{=}\mathrm{CH}{-}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}{-} \xrightarrow[\mathrm{KOH}]{\mathrm{H_2O_2}} >\underbrace{\mathrm{C}{-}\mathrm{C}}_{\mathrm{O}}{-}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}{-}$$

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(1) Preceding publication in this series, M. L. Wolfrom and J. E. Mahan, THIS JOURNAL, **63**, 1253 (1941).

(2) M. L. Wolfrom and A. S. Gregory, *ibid.*, **62**, 651 (1940).

(3) E. Weitz, *Ann.*, **418**, 34 (1919).

(4) E. Weitz and A. Scheffer, *Ber.*, **54B**, 2327 (1921).