of 1 g. of palladinized charcoal,[5] containing 100 mg. of palladium. The reductions were carried out at room temperature in a 100-cc. mechanically shaken bottle attached to a large gas buret. Under these conditions the methyl, ethyl and allyl substituted isopropenyl malonic esters (described in Table I) absorbed 99.3, 99.6 and 97.8% of the theoretical quantity of hydrogen. The reductions required approximately one-half hour. The reduced esters were obtained in 85–90% yield by filtering the catalyst and distilling in vacuum. Ethyl methylisopropylmalonate, b. p. 100–102° (11 mm.), was identified by condensation with urea in the presence of alcoholic sodium ethoxide to give 5-methyl-5-isopropylbarbituric acid, m. p. 188–188.5°,[6] and by saponification with 10% barium hydroxide to methyl isopropylmalonic acid, m. p. 123.5–124.5°.[7] Ethyl ethylisopropylmalonate, b. p. 108–110° (11 mm.), was identified in a similar manner by conversion to 5-ethyl-5-isopropylbarbituric acid, m. p. 201.5–202.5°.[8]

The higher isopropenyl alkyl malonic esters are reduced very slowly with palladium at room temperature, but may be reduced rapidly and quantitatively at 150° over Raney nickel in the micro bomb described by Adkins.[9] Thus 0.02 mole of ethyl butyl isopropenyl malonate in 15 cc. of ethyl alcohol absorbed 99.7% of the theoretical quantity of hydrogen using 1 g. of catalyst. Ethyl butyl isopropyl malonate, b. p. 131–132° (11 mm.), was isolated as the reduction product in 90% yield by filtering and distilling in vacuum.

The esters obtained by the sodium alkylation procedure (B) contain a saturated impurity, which is presumably the corresponding isopropyl alkyl malonic ester, since it is not removed by long shaking with concentrated aqueous ammonia or by fractional distillation. Thus over palladium catalyst as previously described the methyl and ethyl substituted isopropenylmalonic esters prepared by sodium alkylation absorbed only 76 and 72% of the theoretical quantity of hydrogen, respectively.

Summary

Ethyl isopropylidene malonate, $(CH_3)_2C{=}C(COOEt)_2$, forms a sodium derivative (formula I) almost quantitatively by reaction with sodamide in liquid ammonia solution or in inert solvents. By alkylation of this sodium derivative in inert solvents, eight new isopropenyl alkyl malonic esters, $CH_2{=}C(CH_3)C(R)(COOEt)_2$, have been prepared. The sodium derivative has also been prepared by reaction of ethyl isopropylidene malonate with powdered sodium in inert solvents, but about 25% of the ester is reduced during the reaction.

If the sodium derivative is prepared and alkylated in alcoholic solution, the yields of alkylated esters are poor, due to extensive alcoholysis which occurs during the synthesis.

BRYN MAWR, PENNA.

RECEIVED AUGUST 9, 1938

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(5) Hartung, THIS JOURNAL, **50**, 3372 (1928).

(6) Preiswerk, *Helv. Chim. Acta*, **6**, 192 (1923).

(7) Van Romburgh, *Rec. trav. chim.*, **5**, 236 (1886).

(8) Thorp, U. S. Patent 1,255,951; *C. A.*, **12**, 977 (1918).

(9) Adkins, THIS JOURNAL, **55**, 4272 (1933).

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

Interaction between Grignard Compounds and Maleic Acid Derivatives

BY CH. WEIZMANN AND F. BERGMANN

Recently, Tarbell[1] reported on reactions between maleic and dimethylmaleic anhydrides with phenylmagnesium bromide: maleic anhydride reacted with two and three mols of the Grignard compound, respectively, giving phenylbenzoylpropionic acid (I) and desylacetophenone (II, R = C_6H_5). As we have studied some time ago the action of various Grignard compounds on maleic anhydride and dimethyl maleate, in continuation of previous work on other dicarboxylic acid anhydrides, we may be allowed to describe briefly our results. In accordance with Tarbell's results, neither ethylmagnesium bromide nor butylmagnesium bromide or benzylmagnesium chloride gave the expected unsaturated keto acids, $RCOCH{=}CHCOOH$, even when the organometallic compound was added to the anhydride; the keto acids formed apparently react more quickly with the Grignard compounds than maleic anhydride (or dimethyl maleate). The experiments to be described have been carried out, using a large excess (8 mols) of the magnesium derivatives.

Dimethyl maleate reacted under these conditions with 3 mols of each Grignard compound. The reacting products are 1,4-diketones of the general formula (II): they are saturated, do not contain hydroxyl groups, as shown by their negative response to the Zerewitinoff test, and give the pyrrole reaction characteristic for 1,4-diketones. The keto groups, although resistant against the attack of semicarbazide in aqueous ethyl alcohol solution, react upon phenylmagnesium bromide: 6-butyl-5,8-diketododecane (II, R = C_4H_9) gave a crystalline diol (IV), while the corresponding

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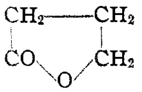
(1) Tarbell, THIS JOURNAL, **60**, 215 (1938).

3-benzyl-1,6-diphenyl-2,5-diketohexane (II, R = $CH_2C_6H_5$) took up only 1 mol of the Grignard compound, yielding (V); obviously, the second keto group is sterically hindered. The formation of the compounds (II) is completely analogous to the occurrence of desylacetophenone reported by Tarbell. The mechanism of the reaction leading to (II) is the following one: the methoxy groups are exchanged by the respective alkyl radicals, and subsequently 1 mol of the Grignard compound is added to the conjugated system, giving the enolate (III) of (II). The inverse order of the steps would not account for the formation of a diketone as primary addition to the conjugated system in dimethyl maleate would give the enolate (VI), which could undergo further alkylation only on one side of the maleate. Theoretically, the enolate (III) could react one-sided with the excess of the Grignard compound; but this reaction may be hindered for steric reasons.[2] In one case the unsaturated diketone, primarily formed according to the above mechanism, reacts with more Grignard compound in 1,2- and not in 1,4-position: from the interaction between dimethyl maleate and butylmagnesium bromide an isomeric tributyl product was secured in small amounts; it contained one hydroxyl group, was unsaturated and, therefore, has to be formulated as (VII). The same substance has been obtained from the analogous reaction with maleic anhydride.

The reaction of *maleic anhydride* upon the three Grignard compounds, in all cases, gave a mixture of acidic and neutral products. The acidic fractions proved homogeneous, they consisted of the respective γ,γ-dialkyl-γ-hydroxycrotonic acids (VIII), which have been characterized by their *p*-phenylphenacyl derivatives. The presence of the tertiary hydroxyl group was proved by the Zerewitinoff method; it causes the easy dehydration of these acids, which makes their purification somewhat tedious. It is rather surprising that phenylmagnesium bromide, according to Tarbell, introduced the two hydrocarbon radicals in a different manner (reaction at one carbonyl group and subsequently at the remaining conjugated system); our observations recall the behavior of phthalic and homophthalic anhydrides.[3] The neutral fractions, deriving from the interaction between maleic anhydride and the Grignard compounds, usually are complicated mixtures from which only the following individual reaction products have been secured: (a) in the case of benzylmagnesium chloride a hydrocarbon of the formula $C_{32}H_{28}$, therefore most probably (IX), the formation of which is analogous to that of tetraphenyldihydrofuran obtained by Purdie and Arup[4] in the case of phenylmagnesium bromide; (b) in the case of butylmagnesium bromide the same substance (VII) which had been isolated as by-product from the corresponding reaction with dimethyl maleate; (c) in the case of ethylmagnesium bromide, a compound $C_{12}H_{24}O_2$, which contains one hydroxyl group and therefore had to be formulated as (X). To the presence of a tertiary hydroxyl group points the inclination of the substance to spontaneous dehydration. The mechanism of the formation of (X) is self-explanatory.

In this connection, experiments on the interaction between butyrolactone (XI) and phenylmagnesium bromide may be mentioned briefly: 2 mols of the Grignard compound gave 1,1-diphenylbutane-1,4-diol (XII).[5]

I $C_6H_5COCH_2CH(C_6H_5)COOH$
II $RCOCH_2CH(R)COR$
III $RC(OMgX)=CHCH(R)COR$
IV $(C_4H_9)(C_6H_5)C(OH)CH_2CH(C_4H_9)C(OH)(C_6H_5)(C_4H_9)$
V $(C_7H_7)(C_6H_5)C(OH)CH_2CH(C_7H_7)COC_7H_7$
VI $CH_3OOCCH(R)CH=C(OMgX)(OCH_3)$
VII $(C_4H_9)_2C(OH)CH=CHCOC_4H_9$
VIII $(R)_2C(OH)CH=CHCOOH$
IX $C_6H_5CH=C(C_7H_7)CH=CHC(C_7H_7)=CHC_6H_5$
X $C_2H_5COCH_2CH(C_2H_5)C(OH)(C_2H_5)_2$
XI



XII $(C_6H_5)_2C(OH)CH_2CH_2CH_2OH$

Experimental

Dimethyl Maleate and Benzylmagnesium Chloride.—The neutral reaction product boiled at 205–210° under 0.05 mm. pressure; on trituration with acetone it solidified and, after recrystallization from alcohol and subsequently from ligroin, formed leaflets, m. p. 136°; yield, 2.0 g. from 7.25 g. (0.05 mol) of dimethyl maleate.

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.3; H, 6.7. Found: C, 84.6; H, 7.0.

3-Benzyl-1,6-diphenyl-2,5-diketo-hexane (II, R = $CH_2C_6H_5$) remained unattacked by concd. sulfuric acid, bromine and by hydrogen in the presence of platinum black

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[2] It is noteworthy that methyl maleate differs from other α,β-unsaturated esters, which add Grignard compounds preferentially in the 1,4-position. Compare Houben-Weyl, "Methoden der organische Chemie," Vol. IV, Leipzig, 1924, p. 840.

[3] *Cf.* ref. 2, p. 850; Weizmann and co-workers, *J. Chem. Soc.*, 1367 (1935); Komppa and Rohrmann, *Ann.*, **509**, 259 (1934).

[4] Purdie and Arup, *J. Chem. Soc.*, **97**, 1537 (1910).

[5] For the analogous reaction of coumarine, see Houben, *Ber.*, **37**, 489 (1904).

in glacial acetic acid solution; the absence of hydroxyl and methoxyl groups was indicated by the micro-Zerewitinoff and the Zeisel methods, respectively.[6]

Reaction with Phenylmagnesium Bromide.—The foregoing substance (0.6 g.) was dissolved in benzene and added to the Grignard solution (prepared from 0.15 g. of magnesium and 1 g. of bromobenzene); the mass was boiled for six hours and then decomposed with ice and dilute sulfuric acid. The reaction product was a viscous oil which crystallized on trituration with acetone and light petroleum. From ligroin (b. p. 130°) 2-hydroxy-5-keto-1,2,6-triphenyl-4-benzylhexane (V) separated in the form of longish plates, m. p. 202°; concd. sulfuric acid gave a brown-red color reaction; yield 250 mg.

Anal. Calcd. for $C_{31}H_{30}O_2$: C, 85.7; H, 6.9. Found: C, 85.7; H, 6.9.

Dimethyl Maleate and Ethylmagnesium Bromide.—The reaction product, 5-ethyl-3,6-diketo-octane (II, R = C_2H_5). boiled at 143° (25 mm.) and 110° (1 mm.).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.5; H, 10.7.

The colorless liquid had $n^{21}\mathrm{D}$ 1.4538, d_{21} 0.9661, hence *MR* = 47.63, while (II, R = C_2H_5) requires 47.27. Hydroxyl and methoxyl groups were absent, the pyrrole test was strongly positive.

Dimethyl Maleate and Butylmagnesium Bromide.—From the neutral reaction product, two homogeneous fractions were obtained by careful fractionation. At 115–120° under 0.1 mm. pressure boiled 5-butyl-5-hydroxy-8-keto-dodecene-(*6*) (VII), which according to its boiling point, refractive index ($n^{18}\mathrm{D}$ 1.4536) and analysis was identical with the neutral product obtained analogously from maleic anhydride.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8, active H, 0.394. Found: C, 75.0, 75.3; H, 11.4, 11.7; active H (micro-Zerewitinoff), 0.483.

The main product, 6-butyl-5,8-diketododecane (II, R = C_4H_9) boiled at 136° under 0.05 mm. pressure; yield 9 g. from 14.4 g. (= 0.1 mole) of dimethyl maleate. *Anal.* Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8. Found: C, 75.2; H, 11.6. It contained no hydroxyl or methoxyl groups, its diketone character was proved by reaction with phenylmagnesium bromide (see below), the 1,4-position of the carbonyl groups by the positive pyrrole test. The molecular refractivity, too, is in accord with (II, R = C_4H_9): $n^{21}\mathrm{D}$ 1.4643; d_{20} 0.9267; hence *MR* = 75.60, while (II, R = C_4H_9) required *MR* = 76.11. **Reaction with Phenylmagnesium Bromide**: The diketone (6 g.) was added to the Grignard solution (from 5 g. of magnesium and 30 g. of bromobenzene). After two hours of boiling, the reaction product was worked up as usual; it distilled at 175–180° under 2.5 mm. pressure; it crystallized partly spontaneously (0.300 g.), from propyl alcohol as leaflets, from light petroleum (80–100°) as stout needles, m. p. 122–123°; concd. sulfuric acid gave an intensely yellow solution. The analysis pointed to formula (IV).

Anal. Calcd. for $C_{28}H_{42}O_2$: C, 81.9; H, 10.2. Found: C, 81.7; H, 10.2. The oily fraction, which has not been obtained analytically pure, is most probably a dehydration product of (IV).

Maleic Anhydride and Benzylmagnesium Chloride.—The acid fraction, boiling under 0.7 mm. at 210–220°, was inhomogeneous, due to partial spontaneous dehydration, but on treatment with *p*-phenylphenacyl bromide the phenylphenacyl ester[7] of γ,γ-dibenzyl-γ-hydroxycrotonic acid (VIII, R = C_7H_7) could be obtained; from propanol it crystallized in stout needles, m. p. 142–143°.

Anal. Calcd. for $C_{32}H_{28}O_4$: C, 80.7; H, 5.9; active H, 0.219. Found: C, 80.6; H, 5.9; active H, 0.211.

The neutral reaction product boiled at 215–220° under 1.5 mm. pressure. It crystallized on trituration with light petroleum and after recrystallization from ligroin (b. p. 130°) formed prisms, m. p. 184°. Combustion analysis proved that 1,6-diphenyl-2,5-dibenzylhexatriene-(1,3,5) (IX) had been formed; maleic anhydride gave no addition product; most probably the ethylenic double bonds are too highly and not asymmetrically enough substituted.[8]

Anal. Calcd. for $C_{32}H_{28}$: C, 93.2; H, 6.8. Found: C, 93.3; H, 6.8.

Maleic Anhydride and Butylmagnesium Bromide.—The acid product after many fractionations had b. p. 114° (0.05 mm.) and consisted of γ,γ-dibutyl-γ-hydroxycrotonic acid (VIII, R = C_4H_9).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.3; H, 10.3; active H, 0.935. Found: C, 67.2; H, 9.8; active H, 0.915. It was characterized by its *p*-phenylphenacyl ester, which after crystallization from light petroleum had m. p. 79°. *Anal.* Calcd. for $C_{26}H_{32}O_4$: C, 76.5; H, 7.8; active H, 0.245. Found: C, 76.0; H, 8.0; active H, 0.265. The neutral product (VII) distilled at 114° under 0.1 mm. pressure; $n^{22.5}\mathrm{D}$ 1.4568; d_{21} 0.9069; yield, 4 g. (from 9 g. of maleic anhydride). *Anal.* Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8; active H, 0.394. Found: C, 76.2; H, 12.2; active H, 0.450.

Maleic Anhydride and Ethylmagnesium Bromide.—γ,γ-Diethyl-γ-hydroxycrotonic acid (VIII, R = C_2H_5), could not be obtained in analytically pure state, due to spontaneous dehydration; the main part of the product distilled at 115° under 0.6 mm. pressure, $n^{21}\mathrm{D}$ 1.4510; d_{21} 1.0170. *Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.8; H, 9.0. Found: C, 62.6; H, 9.5. But this preparation gave a well-defined *p*-phenylphenacyl ester, silky needles from alcohol, m. p. 77–78°. *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 74.7; H, 6.8. From the filtrate of this ester, a second substance, from light petroleum (b. p. 80–100°) as quadratic plates, m. p. 138°, was isolated in minute quantities; it probably is the *p*-phenylphenacyl ester of the corresponding unsaturated γ-ethylsorbic acid.

The neutral fraction had b. p. 75° (112°) under 1.5 (37) mm. pressure; it gave a brown-red color reaction with concd. sulfuric acid. According to the analysis, it consisted of 3-keto-6-hydroxy-5,6-diethyloctane (X). *Anal.* Calcd. for $C_{12}H_{24}O_2$: C, 72.0; H, 12.0; active H, 0.500. Found: C, 73.0; H, 11.3; active H, 0.592. In the same direction points the molecular refractivity: $n^{21}\mathrm{D}$ 1.4574;

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[6] The reaction for 1,4-diketones, carried out according to Knorr [*Ber.*, **19**, 46 (1886)], was strongly positive.

[7] H. Meyer, "Nachweis und Bestimmung organischer Verbindungen," J. Springer, Berlin, 1933, p. 106.

[8] 1,2,3,4-Tetraphenylbutadiene, *e. g.*, does not add "philodienic" compounds. Unpublished results from our laboratories.

d_{21} 0.9269; hence $MR = 58.82$, while (X) requires $MR = 59.15$. We were unable to obtain this substance absolutely free from an impurity of diketonic character, which gave a positive response to the pyrrole test.

Butyrolactone[9] (VIII, 7.5 g.), in ethereal solution was treated with **phenylmagnesium** bromide (prepared from 2.1 g. of magnesium and 13.7 g. of bromobenzene); violent reaction took place. The reaction product, isolated as usual, crystallized spontaneously. By recrystallization from benzene, the needles of 1,1-diphenylbutane-1,4-diol (XII), m. p. 108°, were obtained; yield 2 g. *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4; active H, 0.827. Found: C, 78.9; H, 7.5; active H, 0.728.

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[9] Johansson and Sebelius, *Ber.*, **51**, 4820 (1918), b. p. 104° at 19 mm.

Summary

The reaction between dimethyl maleate and maleic anhydride and Grignard compounds (benzylmagnesium chloride, butylmagnesium bromide, ethylmagnesium bromide) has been studied. Dimethyl maleate gives, by interaction with 3 mols of the organometallic compound, 1,4-diketones of the general formula $RCOCH_2CH(R)COR$, while from maleic anhydride γ,γ-dialkyl-γ-hydroxycrotonic acids and a variety of neutral products are obtained.

The reaction mechanism is discussed.

REHOVOTH, PALESTINE RECEIVED JULY 12, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Influence of α-Halogen Substitution on the Enolization of Ketones

BY E. P. KOHLER[1] AND H. M. SONNICHSEN

Halogen substitution in the α-position is known to promote the enolization of ketones in acid media,[2] but the effect of α-halogen substitution on the enolization of ketones in basic solution has been investigated less extensively. Bartlett's measurements of the rate of bromination and chlorination of acetone in basic solution[3] have indicated that enolization is the rate-controlling step in the reaction of ketones with halogens in the presence of bases, and if this mechanism is correct there can be no doubt that α-halogen substitution promotes enolization in basic media, for in practically every case[4] the only product which can be isolated from the alkaline halogenation of a methyl ketone is a trihalo methyl ketone or its cleavage products. Furthermore, if mono- and dihalomethyl ketones are prepared, they are found to react with halogens in the presence of bases more rapidly than the corresponding unsubstituted ketones.[5]

Direct chemical evidence for the theory that α-halogen substitution promotes enolization of carbonyl compounds is not plentiful. Watson observed that brominated acetones and acetophenones are acidic, but later proved that this acidity was to be ascribed to hydrolysis rather than enolization.[6] Fisher[7] found that several substituted dibromo acetophenones were markedly acidic, but like Watson did not attribute this acidity to enolization.

Thus, all discussion of the influence of α-halogen substitution on the enolization of carbonyl compounds in basic solution has been based on assumptions concerning the mechanism of bromination of ketones. In the experiments with α-bromo-β,β-diphenyl propionyl mesitylene described below, we have found direct chemical evidence in support of the theory that α-halogen substitution promotes the enolization of ketones in basic media, independent of any assumptions concerning the mechanism of the reactions of carbonyl compounds.

Investigations in this Laboratory and elsewhere[8] have indicated that the mesityl radical has a marked influence on the stability of enols; therefore it might be expected that α-bromo-β,β-diphenyl propionyl mesitylene would be a rather easily enolized ketone. One would not expect the influence of the mesityl radical to be strong enough, however, to produce any marked peculiarities in the behavior of a monoketone, so it

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[1] The investigations described in this paper were completed under the direction of Professor Kohler, but the manuscript was prepared for publication by the junior author after Professor Kohler's death.

[2] Watson and Yates, *J. Chem. Soc.*, 3318 (1931); 1207 (1932).

[3] Bartlett, THIS JOURNAL, **56**, 967 (1934).

[4] Fuson has been able to obtain stepwise halogenation in only one case [Bull, Ross and Fuson, *ibid.*, **57**, 764 (1935)].

[5] Fuson, Lewis and DuPuis, *ibid.*, **54**, 1114 (1932).

[6] Watson, Nathan and Laurie, *J. Chem. Phys.*, **3**, 170 (1935); Edwards, Evans and Watson, *J. Chem. Soc.*, 1942 (1937).

[7] Fisher and Walling, THIS JOURNAL, **57**, 1562 (1935).

[8] (a) Kohler and Thompson, *ibid.*, **59**, 886 (1937); (b) Kohler, Tishler and Potter, *ibid.*, **57**, 2517 (1935); (c) Barnes and Green, *ibid.*, **60**, 1549 (1938); (d) Lutz and Wood, *ibid.*, **60**, 705 (1938); (e) Barnes, *ibid.*, **57**, 937 (1935); **60**, 1168 (1938).