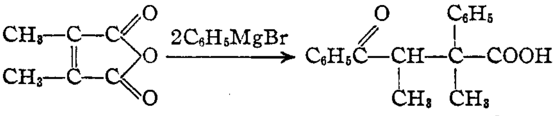
[Contribution from the Department of Chemistry of the University of Rochester]

The Action of Organometallic Compounds on Dimethylmaleic Anhydride

By D. S. Tarbell and Clay Weaver

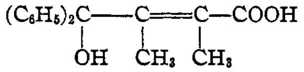
It was reported previously[1] that maleic anhydride yielded a small amount of phenylbenzoylpropionic acid $C_6H_5COCH_2CH(C_6H_5)COOH$ when treated with phenylmagnesium bromide. Dimethylmaleic anhydride under the same conditions gave a good yield of a mixture of two acids. One, melting at 185°, was considered to be 2-phenyl-2-methyl-3-benzoylbutyric acid (II) and the other acid, which was not characterized completely, was regarded tentatively as a stereoisomer of II. Recent work[2] on the action of Grignard reagents on maleic anhydride indicates that structure III is a possible one for the products obtained from phenylmagnesium bromide and dimethylmaleic anhydride. Consequently, a further study of this and analogous reactions seemed desirable.



I

IIa, m. p. 185°

IIb, m. p. 113°

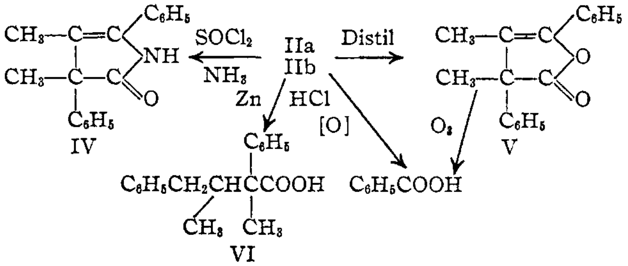


$$(C_6H_5)_2C(OH)-C(CH_3)=C(CH_3)-COOH$$

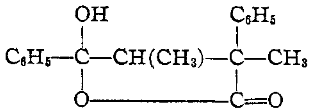
III

The two acids, melting at 184–185° (IIa) and 112–113° (IIb), are shown to be stereoisomeric by the fact that both yield the same lactam IV, on treatment with thionyl chloride and ammonia, and both give the same unsaturated lactone V when distilled under diminished pressure. Furthermore, IIb, on heating with alcoholic alkali, is isomerized to IIa, a process obviously involving epimerization by the alkali of the carbon carrying the hydrogen, with the formation of the more stable isomer IIa.

That the acids have structure II is evident from the following facts. Long-continued reduction of IIa by the modified Clemmensen method[3] yields an acid VI; the slowness of the reaction is doubtless due to the insolubility of the acid in the reaction mixture. Vigorous oxidation of IIa with dichromate gives a 78% yield of benzoic acid, assuming that the benzoic acid can come only from the benzoyl group; the completely substituted carbon alpha to the carboxyl in II would probably not be oxidized.[4] The formation of the lactone V by slow distillation of both IIa and IIb shows that the latter are γ-ketonic acids with a hydrogen adjacent to the carbonyl group[5]; the structure of V for the lactone follows from the fact that it gives tests for unsaturation and on ozonization gives an 83% yield of benzoic acid. This fact is inconsistent with formula VIII for the lactone, which would be derived from the γ-hydroxy acid III. Attempts to prepare a semicarbazone or a dinitrophenylhydrazone from the acid IIa were unsuccessful, but this cannot be considered as valid evidence against structure II, because of the high degree of substitution around the carbonyl group.



The possibility that the acids IIa and IIb might exist in the lactol[6] form VII instead of the open chain form II does not seem likely. The lower-melting acid IIb is readily soluble in carbonate and bicarbonate solution in the cold, and therefore is not a lactol. Since the lower-melting form is isomerized to the higher-melting one by heating with alkali, the latter can hardly be in the lactol form if the former is not.



VII

Attempts, which were unsuccessful, were made to synthesize a compound of structure II by the addition of benzene to the double bond of β-

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[1] Tarbell, This Journal, **60**, 215 (1938).

[2] Weizmann and Bergmann, *ibid.*, **60**, 2647 (1938).

[3] Martin, *ibid.*, **58**, 1438 (1936).

[4] Smith and Prichard, *ibid.*, **62**, 771 (1940).

[5] Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., Inc., New York, N. Y., 1929, p. 359; Adams, Rogers and Sprules, This Journal, **61**, 2819 (1939).

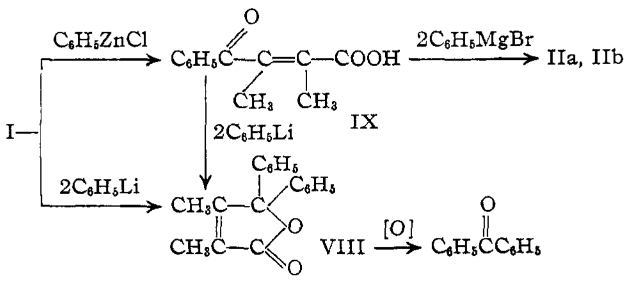
[6] *Cf.* Allen, Normington and Wilson, *Can. J. Research*, **11**, 382 (1934).

benzoyltiglic acid (IX) and its ester. Unsuccessful also were attempts to condense methyl α-chloro-α-phenylpropionate with propiophenone in the presence of sodamide, which should yield II.

The probable mechanism of the addition of two moles of phenylmagnesium bromide to dimethylmaleic anhydride is a splitting of the anhydride ring by one mole of the Grignard, giving the magnesium bromide salt of β-benzoyltiglic acid (IX), followed by a 1,4 addition of the second mole of Grignard to the conjugated system in IX to give IIa and IIb. This mechanism receives strong support from the observation that β-benzoyltiglic acid treated with two moles of phenylmagnesium bromide gave an 86% yield of a mixture of IIa and IIb. Furthermore, β-benzoyltiglic acid was a product of the reaction when one mole of Grignard was used for one mole of anhydride.[1]

The results obtained by treating dimethylmaleic anhydride with phenylzinc chloride and with phenyllithium afford an interesting comparison with the action of the Grignard reagent. Using phenylzinc chloride under the conditions employed with the Grignard reagent, an 8% yield of β-benzoyltiglic acid (IX) was obtained; when the reaction was carried out in boiling benzene a high yield of the same compound was obtained, but in neither case was there evidence for the addition of a second mole of the organometallic compound.

Phenyllithium, under the conditions used with the Grignard reagent, yielded only a trace of IIa; the principal product was a lactone isomeric with V which is assigned structure VIII, since oxidation yields benzophenone as the principal product.



The first step in this reaction is probably an opening of the ring by one mole of phenyllithium, giving the lithium salt of β-benzoyltiglic acid IX. This adds a second mole of phenyllithium 1,2 to form the hydroxy acid III which immediately loses water to give the lactone VIII. In agreement with this, the acid IX when treated with two moles of phenyllithium does yield the lactone.

In preliminary experiments it was found that phenylzinc chloride and succinic anhydride gave a 40% yield of β-benzoylpropionic acid. Phenylmagnesium bromide and succinic anhydride give a mixture of products under the same conditions.[7]

Experimental

Preparation of 2-Phenyl-2-methyl-3-benzoylbutyric Acid (IIa and IIb) by the Action of Two Moles of Phenylmagnesium Bromide on One Mole of Dimethylmaleic Anhydride.—Phenylmagnesium bromide, prepared from 17.3 g. (0.11 mole) of bromobenzene and 2.68 g. (0.11 mole) of magnesium, was added to 6.3 g. (0.05 mole) of dimethylmaleic anhydride in the manner previously described.[1] The fraction soluble in sodium carbonate yielded a mixture of IIa and IIb which was separated by means of the greater solubility of the latter in ether. Recrystallization from benzene–ligroin solution gave IIa, m. p. 183–185°, and IIb, m. p. 112–114°. In one run, a compound melting at 82–84° was isolated. This was regarded as a different crystalline form of IIb, since it gave the same *p*-iodophenacyl ester. The total yield was 3.4 g. of IIa and 8.1 g. of IIb, 81.7% of the theoretical. Analysis of the lower melting isomer agreed with that reported for IIa.[1]

Anal. (IIb).[8] Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.7; H, 6.5.

2-Keto-3,4-dimethyl-3,5-diphenyldihydropyrrole (IV) (Lactam of II).—One gram of the acid (IIa or IIb) was dissolved in an excess of thionyl chloride and refluxed for thirty minutes. The solution was then cooled and added slowly with stirring to a cold solution of concentrated ammonium hydroxide. The white precipitate, when recrystallized from water–alcohol solution, gave needles melting at 67–69°. Unsaturation was indicated by positive tests with aqueous potassium permanganate and bromine–carbon tetrachloride solutions.

Anal. Calcd. for $C_{18}H_{17}ON$: C, 82.1; H, 6.5. Found: C, 82.2; H, 6.2.

2-Keto-3,4-dimethyl-3,5-diphenyldihydrofuran (V, Lactone of II).—The acid (IIa or IIb) was heated in a von Braun flask to a temperature of 220° under a pressure of 20 mm. After fifteen minutes, the temperature was increased to 245–250° and the substance distilled with very little decomposition. The distillate, a colorless oil, when recrystallized from benzene–ligroin solution, gave a crystalline product which melted at 67–68°. It slowly dissolved in hot sodium hydroxide solution and, upon acidification, IIa was obtained. Unsaturation was indicated by positive tests with bromine in carbon tetrachloride and aqueous potassium permanganate solutions. Ozonolysis[9] gave an 83% yield of benzoic acid (identified by means of a

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[7] Komppa and Rohrmann, *Ann.*, **509**, 259 (1934).

[8] Analyses by Dr. L. Weisler.

[9] Houben, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, 1925, Vol. 2, p. 155.

mixed melting point) along with another compound which could not be obtained pure in sufficient quantity for identification.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.5; H, 6.1.

Isomerization of 2-Phenyl-2-methyl-3-benzoylbutyric Acid (IIb).—A small sample (0.5 g.) of IIb was refluxed for two hours with 10% alcoholic sodium hydroxide. After excess alcohol was removed by distillation, the solution was acidified and extracted several times with ether. Evaporation of the dried ether solution left a small amount of solid which crystallized from acetone giving crystals melting at 180–181°. A mixed melting point with pure IIa gave no depression.

2,3-Dimethyl-2,4-diphenylbutyric Acid (VI).—Seven grams of IIa was treated with amalgamated zinc and hydrochloric acid according to the procedure of Martin.[8] After refluxing for twenty-four hours a test sample showed that very little reduction had taken place. Consequently, the treatment was continued for four days, during which two additions of fresh amalgamated zinc were necessary. When the reaction mixture was cooled to room temperature, crystals formed which proved to be starting material (2.5 g.). After drying, the toluene layer was evaporated to 20 cc. Upon cooling, 3.5 g. of a white solid was obtained, which melted at 177–178° after recrystallization from toluene–ligroin solution. A mixed melting point with IIa showed a depression of 25–30°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.61; H, 7.46. Found: C, 80.55; H, 7.45.

Oxidation of 2-Methyl-2-phenyl-3-benzoylbutyric Acid (II).—Two grams of IIa was added to a mixture of 15 cc. of water, 8 g. of sodium dichromate, 10 cc. of concentrated sulfuric acid and 25 cc. of glacial acetic acid. After refluxing for two hours, the acetic acid was removed by distillation and the mixture was filtered while hot. After cooling, 0.67 g. of benzoic acid was obtained which, after recrystallization from water, did not depress the melting point of an authentic sample. The total yield (0.67 g.) was 78% of the theoretical amount, assuming only the benzoyl group is oxidized to benzoic acid.

Action of Phenylmagnesium Bromide on β-Benzoyltiglic Acid.—An ether solution of Grignard reagent, prepared from 1.3 g. (0.054 mole) of magnesium and 8.5 g. (0.054 mole) of bromobenzene, was added at room temperature to a well-stirred solution of 5 g. (0.0244 mole) of β-benzoyltiglic acid (IX) in 200 cc. of absolute ether. During the addition, a precipitate formed immediately as each drop struck the solution. After the addition was complete, the mixture was stirred for one-half hour, at which time a negative test was obtained with Michler ketone.[10] The precipitate was decomposed with ice and 10% sulfuric acid, and the resulting solution worked up in the usual way. The acidic fraction yielded 5.9 g. (85.5%) of material which was a mixture of approximately equal amounts of IIa and IIb.

β-Benzoyltiglic Acid (IX).—Phenylzinc chloride was prepared in the usual way from 20.8 g. (0.15 mole) of freshly fused zinc chloride and 0.15 mole of Grignard reagent.[1] Two hundred cc. of C. P. benzene was added and, after refluxing a few minutes, the mixture was subjected to distillation until the boiling point reached 75°. Another 200-cc. portion of C. P. benzene was added and the reaction mixture was heated to the reflux temperature. Dimethylmaleic anhydride (8.7 g., 0.069 mole) in 100 cc. of C. P. benzene was added dropwise over one hour while stirring the boiling solution. Refluxing was continued for an additional three hours, during which the reaction mixture became pale yellow. The precipitate was decomposed with ice and 10% sulfuric acid. Acidification of the sodium carbonate extracts of the benzene layer gave practically a quantitative yield of IX, m. p. 90–92°. Recrystallization from hot water gave 11.7 g. (83%) of pure benzoyltiglic acid, m. p. 92–93°. A mixed melting point with a sample prepared by the Friedel–Crafts reaction[11] showed no depression.

2,3-Dimethyl-4,4-diphenylcrotonolactone (VIII).—Phenyllithium was prepared by the procedure of Gilman, Zoellner and Selby[12] from 1.53 g. (0.22 mole) of lithium and 17.3 g. (0.11 mole) of bromobenzene. Dimethylmaleic anhydride (6.3 g., 0.05 mole) in 150 cc. of absolute ether was added dropwise to the well-stirred solution at room temperature. A steady current of dry nitrogen was allowed to flow through the system during the entire reaction. After all the anhydride had been added, the reaction mixture was stirred for one hour at room temperature, followed by an additional hour under reflux. After cooling, ice and 10% sulfuric acid were added. The acid produced a precipitate in the water layer which dissolved in the ether layer. Acid was added until this transient precipitate no longer appeared. This mixture was worked up in the usual way, the acidic fraction yielding but a trace (0.1 g.) of an acid identical with IIa. The ether solution of the neutral fraction was dried and evaporated under reduced pressure, leaving 10.9 g. (84.4%) of an oil which would not crystallize. The oil was extracted with three 15-cc. portions of hot petroleum ether (b. p. 60–70°), which on cooling yielded 2.7 g. of crystalline material melting at 89–90°. The residual oil (8 g.) was distilled under reduced pressure, giving 6.2 g. of a clear oil which crystallized from petroleum ether (b. p. 60–70°) and was identical with the compound above, m. p. 89–90°. The total yield of crystalline material was 67.5% of the theoretical. Unsaturation was indicated by slow decolorization of aqueous potassium permanganate solution, but the bromine–carbon tetrachloride test was negative. Oxidation with chromic acid gave a 72% yield of benzophenone which was characterized by means of a mixed melting point.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.10. Found: C, 81.7; H, 6.14.

Action of Phenyllithium on β-Benzoyltiglic Acid.—Phenyllithium, prepared from 1.3 g. (0.19 mole) of lithium and 14.1 g. (0.09 mole) of bromobenzene, was allowed to react with 8.2 g. (0.04 mole) of β-benzoyltiglic acid under the same conditions employed in the analogous reaction with dimethylmaleic anhydride. The ether layer yielded 9.8 g. of a neutral oil and 0.6 g. of material soluble in sodium carbonate. The neutral fraction, when treated in the manner described above, yielded a total of 6 g. of VIII

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[10] Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

[11] Lutz and Taylor, *ibid.*, **55**, 1593 (1933).

[12] Gilman, Zoellner and Selby, *ibid.*, **54**, 1957 (1932).

(57%). The acid fraction yielded a trace of IIa when recrystallized from alcohol.

Summary

1. The action of two moles of phenylmagnesium bromide on dimethylmaleic anhydride yields a mixture of two stereoisomeric acids, which have been shown to be 2-phenyl-2-methyl-3-benzoylbutyric acids.

2. The probable mechanism of their formation involves a splitting of the anhydride ring by one mole of phenylmagnesium bromide, followed by 1,4 addition of a second mole to the unsaturated keto acid formed. Evidence to support this mechanism is presented.

3. Phenylzinc chloride reacts with dimethylmaleic anhydride to give a high yield of β-benzoyltiglic acid, but shows no tendency to add a second mole.

4. Phenyllithium gives 2,3-dimethyl-4,4-diphenylcrotonolactone, which probably results from 1,2 addition of a second mole of organometallic compound to the intermediate unsaturated keto acid. Only a small amount of material resulting from 1,4 addition is formed.

5. Phenylzinc chloride and succinic anhydride give a 40% yield of β-benzoylpropionic acid.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of 6-Hydroxy-17-equilenone (an Isomer of Equilenin) and Two of its Homologs

BY W. E. BACHMANN AND D. W. HOLMES[1]

Inasmuch as the procedures worked out for the synthesis of equilenin[2] appeared applicable to the preparation of homologs and isomers of the sex hormone, we were in a position of being able to secure information in regard to the effect of varying the structure of the molecule on the estrogenic activity. As part of this program, we prepared desoxyequilenin and desoxyisoequilenin,[3] which possess the same structure as equilenin except for the hydroxyl group. The method has been extended now to the synthesis of an isomer of equilenin which differs from the sex hormone only in having the hydroxyl group on C_6 instead of on C_3. According to the nomenclature proposed by us recently,[3] the compound is called 6-hydroxy-17-equilenone (I). In virtue of the asymmetric carbon atoms C_{13} and C_{14}, the compound can exist in *cis* and *trans* forms, both of which are racemic mixtures. We have synthesized the *cis dl* and *trans dl* forms of 6-hydroxy-17-equilenone, but have made no attempt to resolve them at this time.

As starting material for the synthesis, we employed the 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene (II) of Kon and Ruzicka,[4] which can be prepared readily from the methyl ether of α-naphthol. The steps involved in the synthesis are exactly analogous to those employed in the preparation of equilenin, and consist in the introduction of a carbomethoxy group in position 2 through the glyoxalate reaction, the introduction of a methyl group to give III, the reaction of this compound with zinc and methyl bromoacetate, the dehydration of the Reformatsky ester and the reduction of the unsaturated acids to the reduced acids (VI), which were separated into the *cis* and *trans* forms. Since the configurations of these acids are not yet known, they are distinguished by the prefixes α and β, and the compounds synthesized from them are known as α- and β-6-hydroxy-17-equilenone, respectively, it being understood that one of them is the *cis* and the other the *trans* form. The formation of the latter compounds was accomplished by lengthening the acetic acid side-chain of the reduced acids to the propionic acid group by means of the Arndt–Eistert reaction, cyclizing the product and hydrolyzing, decarboxylating and demethylating the cyclic compound. Inasmuch as the formulas of the intermediates are exactly like those of the equilenin synthesis except for the position of the hydroxyl group, the formulas are not reproduced here with the exception of a few that require further mention.

It is of interest that hot methanolic potassium hydroxide strips the carbomethoxy group from

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[1] From the Ph.D. dissertation of D. W. Holmes.

[2] Bachmann, Cole and Wilds, THIS JOURNAL, **61**, 974 (1939); **62**, 824 (1940).

[3] Bachmann and Wilds, *ibid.*, **62**, 2084 (1940).

[4] Kon and Ruzicka, *J. Chem. Soc.*, 187 (1936).