of a starch fraction. Equations are given for estimating accurately the intrinsic viscosities of amyloses and amylopectins in 1 N KOH solution from relative viscosities taken at 0.2% concentration. Iodine affinities of these same alkaline solutions are determined potentiometrically, to measure the proportion of linear material in the starch fractions. Experimental data are presented illustrating the validity of the procedure.

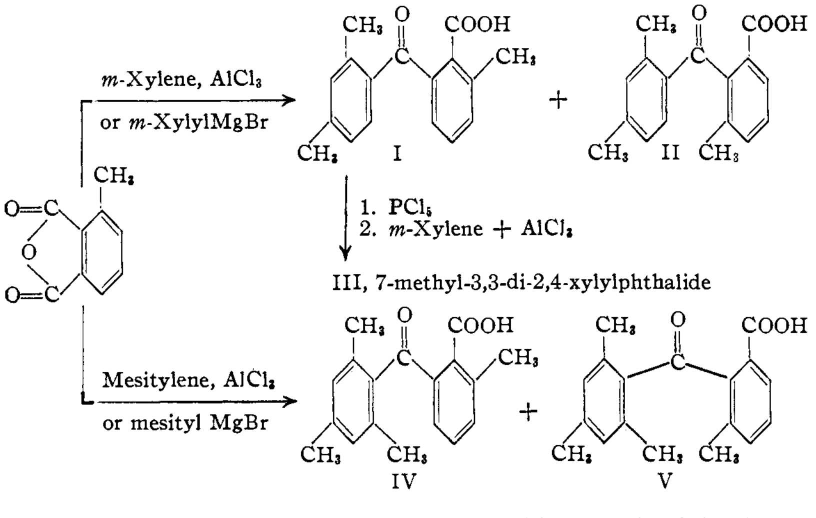
PEORIA, ILL. RECEIVED APRIL 21, 1950

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

The Behavior of 3-Methylphthalic Anhydride in Friedel–Crafts and Grignard Condensations. II[1]

BY MELVIN S. NEWMAN AND CHESTER W. MUTH

In a previous publication the condensations of 3-methylphthalic anhydride with benzene and with phenylmagnesium bromide were described.[2] We report here on the condensations of this unsymmetrical anhydride with *m*-xylene, mesitylene, *m*-xylylmagnesium bromide and mesitylmagnesium bromide. These reactions are outlined in the chart and the results of this and previous[2] work are summarized in Table I.



Inspection of the results recorded in Table I reveals that the ratio of isomeric ketoacids formed is markedly affected by the reagent. The greater the number of methyl groups ortho to the position at which condensation with the anhydride occurs the greater the preference for reaction away from the methyl group in the anhydride. The Grignard condensations are more sensitive to this effect than the Friedel–Crafts condensations. The question as to how much of this effect is due to polar and how much to steric effects cannot be answered by these experiments but the results may be of use in predicting the ratio of products in other reactions of unsymmetrical anhydrides.

The methods used for separating I and II from their mixtures and for IV and V are of interest. Mixtures of I and II were esterified with diazomethane and the mixture of normal methyl esters of I and II thus obtained dissolved in concentrated sulfuric acid. After a short time the solution was poured on ice. The acid fraction proved to be almost pure I while the neutral fraction was the methyl ester of II. This finding may be explained by postulating a complex ionization in sulfuric acid of the methyl ester of I[3] whereas the methyl ester of II undergoes simple ionization.

The separation of IV and V was accomplished by taking advantage of the fact that IV esterifies much more slowly than V and that the methyl ester of IV saponifies under alkaline conditions much more slowly than the methyl ester of V.

Experimental

The values listed in Table I do not necessarily represent a single experiment. Rather we have tried to give a value which we believe to be most accurate. All reactions were run several times and the values indicated are taken from two or more checking experiments. Typical Friedel–Crafts and Grignard reactions are described below.

Reactions of 3-Methylphthalic Anhydride. (a) With Grignard Reagents.—To a well-stirred solution of 8 g. of 3-methylphthalic anhydride[2] in 80 ml. of benzene and 80 ml. of ether was added one equivalent of about 1.0 M Grignard reagent (titrated). After stirring at room temperature for fifteen minutes the mixture was hydrolyzed with 30 ml. of concentrated hydrochloric acid and separated into acidic and neutral fractions. The crude acids, I and II, thus obtained are listed in Table I. The neutral material was not examined as it amounted to less than 5% and was obviously a mixture. Analytical samples of I and II were obtained by recrystallization of portions of I and II isolated as described below. I melted at 118.4–119.5°, and II at 176.2–178.0°.

Anal.[4] Calcd. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0. Found: (I) C, 76.1; H, 5.7; (II) C, 75.9; H, 6.1.

In a similar way, analytical samples of IV and V were obtained from samples of IV and V isolated as described

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[1] Taken from the Ph.D. thesis of C. W. M., 1949. Chemistry Department, University of West Virginia, Morgantown, W. Va.

[2] M. S. Newman and C. D. McCleary, THIS JOURNAL, **63**, 1542 (1941).

[3] M. S. Newman, R. A. Craig and A. B. Garrett, *ibid.*, **71**, 869 (1949), equation 15.

TABLE I

BEHAVIOR OF 3-METHYLPHTHALIC ANHYDRIDE IN FRIEDEL–CRAFTS AND GRIGNARD CONDENSATIONS

	Reagent	Crude acids, yield, %	Reacn. at unhindered[a] carbonyl, yield, %[b]	Reacn. at hindered[a] carbonyl, yield, %[b]	Approx. ratio of unhindered[a] to hindered[a] reacn.[c]
1	Benzene[2]	80	38	37	1:1
2	*m*-Xylene	82	42[d]	32	4:3
3	Mesitylene	95	68	16	4:1
4	C_6H_5MgBr[2]	76	43	14	3:1
5	a. *m*-$(CH_3)_2C_6H_3MgBr$	77	39	4	10:1
	b. *o*-$CH_3C_6H_4MgBr$[2]	78	47	5	10:1
6	*sym*-$(CH_3)_3C_6H_2MgBr$	85	66	1	66:1

[a] The terms unhindered and hindered are used to denote the carbonyl distant from and adjacent to the methyl group in 3-methylphthalic anhydride, respectively. However, we do not subscribe to the view that the results are determined entirely by steric effects since polar effects may also be involved. [b] The yields reported in these columns are calculated on the basis of starting 3-methylphthalic anhydride and represent material of considerable purity. The experiments were repeated enough to be sure that the yields cited are representative for our conditions. [c] Since the reaction mixtures were not analyzed quantitatively for isomer composition these ratios are only approximate. However, we feel that they represent the true ratio fairly closely. [d] Part of this percentage represents the quantity of the phthalide, III, formed from I during the reaction.

below. IV melted at 218.8–220.5° (benzene) and V at 208.0–209.6° (80% ethanol).

Anal.[4] Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: (IV) C, 76.3, 76.8; H, 6.4, 6.5; (V) C, 76.6; H, 6.3.

(b) **Friedel–Crafts.**—A slight excess of aluminum chloride (Ohio Apex) was added to a solution of 8 g. of the anhydride in 60 ml. of the reacting hydrocarbon. Stirring at room temperature for three hours proved desirable in the case of *m*-xylene whereas heating at 70–80° for 45 minutes was the choice with mesitylene. After pouring on ice and hydrochloric acid, the acid and neutral fraction were separated as usual. In the reactions involving *m*-xylene from 3 to 25% of phthalide, III was isolated from the neutral fraction. Since III results from further condensation of I, the per cent. of III was always added to the per cent. of I isolated for the purpose of calculating reaction at the "unhindered" carbonyl. No similar phthalide was obtained from reactions with mesitylene. Phthalide, III, was prepared in good yield by heating a mixture of the acid chloride (undoubtedly pseudo acid chloride) from 2 g. of I, 25 ml. of *m*-xylene and 1.5 g. of aluminum chloride at 70° for one hour. On pouring on ice, III was obtained as colorless crystals, m. p. 171–173°, from benzene.

Anal.[4] Calcd. for $C_{25}H_{24}O_2$: C, 84.2; H, 6.8. Found: C, 84.5; H, 7.2.

Separation of Isomeric Acids. (a) 2-*m*-Xyloyl-6-methylbenzoic Acid (I) and 2-*m*-Xyloyl-3-methylbenzoic Acid (II).—The crude mixture of acids obtained from a typical Friedel–Crafts reaction was dissolved in dry ether and treated with ethereal diazomethane. The ester mixture thus obtained, 13.3 g., was diluted with 5 ml. of dry sulfur-free benzene and treated with 100 ml. of 100% sulfuric acid. The mixture turned dark red at once and the temperature rose to 40–50°. After eight minutes this mixture was poured on ice and separated into acid and neutral fractions. After two crystallizations of the acid fraction from benzene–petroleum ether (b. p. 65–110°) there was obtained 4.48 g. (34% based on starting 3-methylphthalic anhydride) of I, m. p. 113.5–115.5°.[5] From the neutral fraction of the original Friedel–Crafts reaction mixture there was isolated 4% of the phthalide, III, thus making a total yield of 38% of products resulting from reaction at the "unhindered" carbonyl group.

The neutral fraction from the above sulfuric acid treatment was crystallized from a small amount of methanol to yield 4.05 g. (29%) of the normal methyl ester of II, m. p. 57–60°.[5]

(b) 2-Mesitoyl-6-methylbenzoic Acid (IV) and 2-Mesitoyl-3-methylbenzoic Acid (V).—In a typical separation 26.67 g. (representing a 95% yield of keto acids from a Friedel–Crafts reaction) of acids, m. p. 170–202°, was dissolved in 250 ml. of methanol saturated with hydrogen chloride and the solution was refluxed for three hours. The acid fraction, m. p. 217.5–219.5° after sintering at 208°, thus obtained was further refluxed with methanolic hydrogen chloride for an additional fourteen hours. The acid fraction, 18.38 g. (65% based on starting 3-methylphthalic anhydride) then melted at 218.5–220.4° after sintering at 215°, and was almost pure IV. The ester fraction obtained from the above methanol treatments was refluxed in a solvent consisting of 100 ml. of 0.47 *N* potassium hydroxide in ethylene glycol and 50 ml. of methanol for four hours, after which the methanol was distilled. The residue was poured into water and the acid fraction was crystallized from benzene to yield 4.56 g. (16% based on 3-methylphthalic anhydride) of V, m. p. 206–208°. The neutral fraction from this saponification yielded 0.50 g. (3%) of the crystalline methyl ester of IV, m. p. 110.5–112.0°.[5]

Proof of Structure of Keto Acids.—The structures assigned to I, II, IV and V were established by analysis, titration for molecular weight, and decarboxylation to ketones. The decarboxylations were accomplished in good, but not exactly determined, yield essentially as described previously.[6] Comparison of the ketones with authentic samples was effected either by the method of mixed melting points using the ketone, if solid, or the 2,4-dinitrophenylhydrazone. I yielded 2,3′,4-trimethylbenzophenone, m. p. 40.2–41.2° (crystallization from ether and from methanol at −30°). The authentic ketone, b. p. 158–160° at 2 mm., was prepared by reaction of *m*-xylylmagnesium bromide with *m*-tolunitrile.[7]

Anal.[4] Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.7; H, 6.9.

II yielded 2,2′,4-trimethylbenzophenone,[8] a liquid, b. p. 143–148° at 1 mm. The red 2,4-dinitrophenylhydrazone melted at 233–235° after four crystallizations from pyridine.

Anal.[4] Calcd. for $C_{22}H_{20}O_4N_4$: C, 65.3; H, 5.0; N, 13.9. Found: C, 65.3; H, 4.6; N, 14.0.

IV yielded 2,3′,4,6-tetramethylbenzophenone,[9] m. p. 65.5–67.5°, and V yielded 2,2′,4,6-tetramethylbenzophenone, m. p. 109.6–111.6°. The authentic sample was prepared by a Friedel–Crafts condensation of a *o*-toluyl chloride with mesitylene in excess hydrocarbon as solvent.

Anal.[4] Calcd. for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 86.0; H, 7.5.

Summary

The reactions of 3-methylphthalic anhydride with benzene, *m*-xylene and mesitylene (Friedel–

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[4] We are indebted to Mrs. E. H. Klotz for these analyses.

[5] The melting point of this material is not as high as the purest sample but the yield reported is probably fairly accurate since the loss on recrystallizing this material to its highest melting point could be made up by further working on the original mother liquors.

[6] M. S. Newman and C. D. McCleary, THIS JOURNAL, **63**, 1537 (1937).

[7] C. Seer, *Monatsh.*, **32**, 143 (1911), reported this ketone as an oil formed by reaction of *m*-toluyl chloride with *m*-xylene. A poor analysis of a dark oil was reported.

[8] A. W. Smith, *Ber.*, **24**, 4050 (1891).

[9] R. C. Fuson, *et al.*, THIS JOURNAL, **64**, 2573 (1942). We wish to thank Dr. Fuson for supplying us with a sample of this ketone.

Crafts) and with phenyl-, *m*-xylyl- and mesitylmagnesium bromides are summarized. The condensation with the 1-carbonyl group in the anhydride increases as the number of methyl groups ortho to the new point of attachment increases. This effect is considerably more noticeable in the Grignard reactions than in the Friedel–Crafts.

COLUMBUS, OHIO RECEIVED JUNE 9, 1950

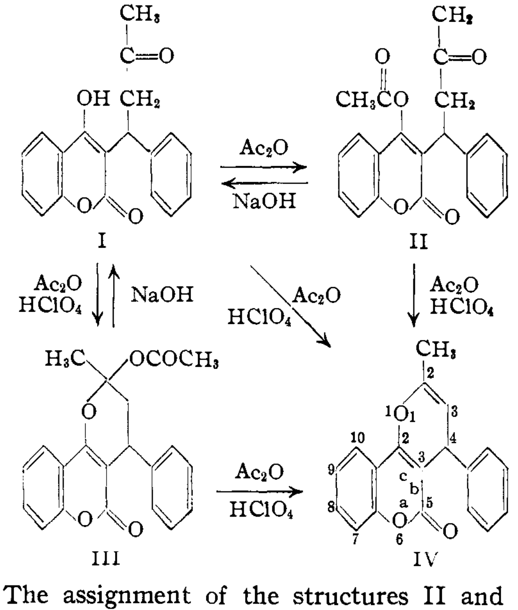
[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. X. Acylation of 3-(α-Phenyl-β-acetylethyl)-4-hydroxycoumarin[1]

BY MARTIN SEIDMAN, DALE N. ROBERTSON AND KARL PAUL LINK

Shortly after the anticoagulant 3,3′-methylenebis-(4-hydroxycoumarin), (Dicumarol®), was isolated from spoiled sweet clover hay,[2] identified and synthesized,[3,4] its marked toxicity in the rat was noted.[5] It was also indicated[6] that many other 3-substituted-4-hydroxycoumarins possess powerful *in vivo* anticoagulant activity in many animal species and a complete account of their relative activity in the rabbit has been published.[7] Recently, O'Connor reported the successful use of Dicumarol® as a rodenticide.[8] It was felt desirable therefore to restudy the more potent compounds in the rat especially for rodenticidal potentialities. The results of this survey[9] revealed that 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin (I) is approximately fifty times more lethal and in addition the time to effect kill is about half that required by Dicumarol®. A study of the reactions of I was consequently undertaken. This paper reports an improved synthesis and various ester derivatives.

I is prepared by a Michael addition of 4-hydroxycoumarin to benzalacetone.[10] By refluxing the reactants in dioxane containing piperidine as catalyst for four hours a yield of 67% of pure product has been realized. Acetylation of I under different conditions has produced three derivatives. When I is refluxed with acetic anhydride the acetate II, m. p. 117–118°, is obtained. If, however, I is treated with acetic anhydride containing perchloric acid as catalyst the acetate III, m. p. 204–205°, can be isolated in small yield. By allowing this reaction to proceed for five minutes the dehydrated product 2 - methyl - 4 - phenyl - 5 - oxo - γ - pyrano - (3,2-c)(1)-benzopyran (IV) crystallizes out. This dehydration parallels that of 4-salicylbutan-2-one to form 2-methylchromene.[11]



The assignment of the structures II and III is based upon the following considerations:

1. The compound with the higher melting point is assumed to be the more symmetrical and have the more rings.

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[1] Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. This work is from the thesis submitted by Martin Seidman to the faculty of the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, July, 1950. This paper was presented before the Division of Organic Chemistry at the 117th Meeting of the American Chemical Society, Philadelphia, April, 1950. Subsequent to the submission of this paper, the coined name "warfarin" was assigned to the Anticoagulant Rodenticide 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin, S. A. Rohwer, U. S. Dept. Agr. Interdepartmental Comm. Pest Control, June 29, 1950. The chemical name 3-(α-acetonylbenzyl)-4-hydroxycoumarin is the systematic name selected by *Chemical Abstracts* for warfarin.

[2] H. A. Campbell and K. P. Link, *J. Biol. Chem.*, **138**, 21 (1941).

[3] M. A. Stahmann, C. F. Huebner and K. P. Link, *ibid.*, **138**, 513 (1941).

[4] K. P. Link, *Harvey Lecture Series*, **39**, 162 (1943–1944).

[5] R. S. Overman, J. B. Field, C. A. Baumann and K. P. Link, *J. Nutrition*, **23**, 589 (1942).

[6] R. S. Overman, M. A. Stahmann, W. R. Sullivan, C. F. Huebner, H. A. Campbell and K. P. Link, *J. Biol. Chem.*, **142**, 941 (1942).

[7] R. S. Overman, M. A. Stahmann, C. F. Huebner, W. R. Sullivan, L. Spero, D. G. Doherty, M. Ikawa, L. Graf, S. Roseman and K. P. Link, *ibid.*, **153**, 5 (1944).

[8] J. A. O'Connor, *Research*, **1**, 334 (1948).

[9] By Dr. Lester D. Scheel and Mrs Dorothy W. Ballou. A complete account of this survey is in the Masters thesis of Dorothy L. Wu, Biochemistry Department, University of Wisconsin, 1949. Recent unpublished findings in this laboratory have shown that less than a total of 1.0 mg. of 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin administered daily will kill the average 250-g. laboratory rat in five to ten days.

[10] M. Ikawa, M. A. Stahmann and K. P. Link, THIS JOURNAL, **66**, 902 (1944).

[11] W. Baker and J. Walker, *J. Chem. Soc.*, 646 (1935).