

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

The Behavior of 3-Methylphthalic Anhydride in Friedel-Crafts and Grignard Condensations^{1,2}

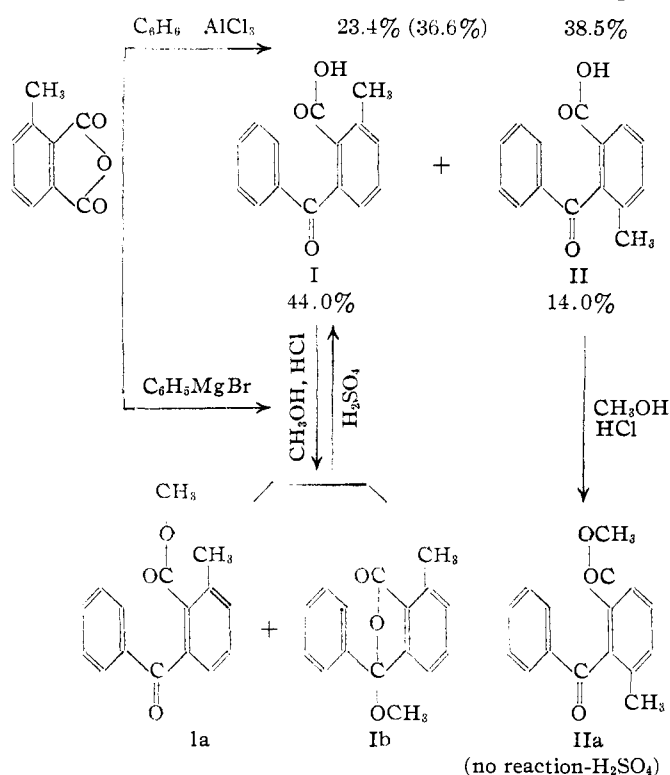
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For some time we have been interested in the reactions of unsymmetrically substituted anhydrides of the *o*-phthalic type. In particular, we desired information concerning the relative amounts of isomeric 2-benzoylbenzoic acids formed when such anhydrides are treated with Grignard reagents or react with aromatic derivatives in the Friedel-Crafts condensation.

In our experience, Grignard reagents, especially those containing an ortho substituent, react preferentially with the unhindered carbonyl group of such anhydrides.³ This behavior is to be expected if one bears in mind the effect of steric hindrance on the Grignard reaction. Little information, however, is available concerning the course of reaction in the case of the Friedel-Crafts condensation, and it is not known to what extent, if any, steric hindrance affects this reaction. For example, it is reported that in condensations using benzene, 3-acetylaminophthalic anhydride yields 51% of 2-benzoyl-3-aminobenzoic acid and a small quantity of 2-benzoyl-6-aminobenzoic acid,⁴ 3-bromophthalic anhydride yields 89% of 2-bromo-6-benzoylbenzoic acid,⁵ and 3-methylphthalic anhydride yields 9.7% of 2-benzoyl-6-methylbenzoic acid, I, and 36.8% of 2-benzoyl-3-methylbenzoic acid, II.⁶

Since we desired a supply of I and II in connection with the problem presented in the preceding article,⁷ we decided to study the behavior of 3-methylphthalic anhydride in both Friedel-Crafts and Grignard reactions. In both instances mixtures of I and II were formed which were difficult to separate by fractional crys-

tallization. However, by taking advantage of the fact that both the normal and pseudo methyl esters of I are rapidly hydrolyzed in concentrated sulfuric acid whereas the normal methyl ester of II is largely unaffected,⁷ a method was developed whereby these mixtures could be analyzed with relatively little loss. The method is outlined and the results are summarized in the chart below. The experi-



mental details are briefly described under the experimental part and a complete account is available in the thesis of C. D. McCleary at The Ohio State University.⁸

The relative amounts of acids formed in the Grignard reaction afford further evidence of the effect of steric hindrance on the course of this

(1) The material herein presented formed part of the dissertation presented by C. D. M. to The Ohio State University in partial fulfillment of the requirements for the Ph.D. degree, June, 1940.

(2) Presented before the Organic Division at the Detroit meeting of the American Chemical Society, September, 1940.

(3) (a) Fieser and Newman, *THIS JOURNAL*, **58**, 2376 (1936); (b) Newman, *ibid.*, **59**, 1003 (1937); (c) Newman and Orchin, *ibid.*, **60**, 586 (1938); **61**, 244 (1939); (d) Newman, *ibid.*, **60**, 1368 (1938).

(4) Lawrence, *ibid.*, **42**, 1871 (1920).

(5) Stephens, *ibid.*, **43**, 1950 (1921).

(6) Hayashi, *et al.*, *Bull. Chem. Soc. Japan*, **11**, 184 (1936). The calculations of percentage yields are ours.

(7) Newman and McCleary, *THIS JOURNAL*, **63**, 1537 (1941).

(8) It is of interest to point out that this method should prove of great value in improving the general method for synthesis of substituted 1,2-benzanthracenes originally developed by Fieser and Newman (reference 3a). The separation of the desired isomer from the mixture of keto acids formed in the first step by condensation of aromatic Grignard reagents with 1,2-naphthalic anhydride has generally proved time consuming and the yields are often low. The new method should simplify the procedure and thereby increase the yields.

reaction. Of the acids isolated in the Friedel-Crafts condensation, 23.4% consisted of I and 38.5% of II.⁹ However, in the Friedel-Crafts reactions an appreciable amount of a neutral substance also was formed. This neutral product was shown to be 2,2-diphenyl-6-methylphthalide, III, by synthesis from 2-benzoyl-6-methylbenzoic acid, I, and two molecules of phenylmagnesium bromide. Taking into account the fact that phthalide must be formed at the expense of I, the values become 36.6% of I and 38.5% of II. It would thus appear that steric hindrance is not a major factor in this reaction.

In order to prepare the 3-methylphthalic anhydride required we have studied the dehydrogenation of 3-methyl-1,2,3,6-tetrahydrophthalic anhydride.¹⁰ On heating with palladium-charcoal¹¹ at 270–320° or with a nickel-on-kieselguhr catalyst¹² at 350–370° about 50% of the theoretical amount of hydrogen was evolved but none of the desired product was obtained. On refluxing the tetrahydro anhydride with lead tetraacetate in acetic acid a very small amount of 3-methylphthalic anhydride was isolated.¹³ Dehydrogenation using sulfur^{10c} was more successful, yields running near 50%, but considerable crystallization and distillation were required to secure a sulfur-free product. The best procedure involved heating with bromine in acetic acid followed by pyrolysis of a bromine-containing intermediate. In one case 73% of pure 3-methylphthalic anhydride was obtained. We feel that the process can be improved and further work in this connection is being done.

Experimental¹⁴

3 - Methyl - 1,2,3,6 - tetrahydrophthalic Anhydride.—In the best of several experiments 34 g. of piperylene,¹⁵ b. p. 41–41.5°, was added slowly with cooling (below 10°) to a solution of 65.7 g. (33% excess) of freshly distilled maleic anhydride in 360 cc. of dry benzene. After standing at 5–10° for twenty days, the benzene was removed under reduced pressure and the remaining yellow liquid separated

(9) The results of the Friedel-Crafts condensation were averaged in obtaining these values.

(10) (a) Diels and Alder, *Ann.*, **470**, 62 (1929); (b) Farmer and Warren, *J. Chem. Soc.*, 3221 (1931); (c) Newman, *THIS JOURNAL*, **59**, 1003 (1937).

(11) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

(12) Obtained from the Universal Oil Products Company through the courtesy of Dr. A. L. Henne of this Department.

(13) Compare Newman, *THIS JOURNAL*, **62**, 1683 (1940), and references on this subject therein.

(14) All melting points corrected. All benzene used in reactions was freed of thiophene by stirring with concentrated sulfuric acid followed by distillation.

(15) Impure piperylene, b. p. 38–41°, gave a 59% yield of crystalline addition product in a similar experiment.

by distillation at 5 mm. into 24.5 g. of a fore-run, b. p. 60–131°, consisting mostly of maleic anhydride, and 67.8 g. (81.5%) of crystalline material, b. p. 131–134°. This product is suitable for further use but may be recrystallized with little loss from benzene-ligroin to yield material melting at 59–62°. Four of such condensations averaged $80 \pm 2.5\%$ of crystalline distillate. Condensations under similar conditions using 0, 3, 10, and 40% excess maleic anhydride gave 70, 70, 74, and 80.6% yields.

3-Methylphthalic Anhydride.—The best procedure we have found to date is as follows. To a solution of 50 g. of the above addition product in 100 cc. of glacial acetic acid just below the boiling point was added dropwise a solution of 124 g. of bromine in 110 cc. of acetic acid during one hour. The first third of the bromine solution was decolorized immediately and some hydrogen bromide was evolved. After sixteen hours of refluxing the solution was concentrated under reduced pressure and the residue heated at 210–220° for nine hours during which time much hydrogen bromide was evolved and the material became quite dark. On distillation at 2 mm., there was obtained a colorless liquid, b. p. 174–176°, which immediately crystallized. Crystallization from benzene-petroleum ether yielded 35.7 g. (73%) of 3-methylphthalic anhydride, m. p. 114.5–117.0°. The solvent was removed from the mother liquor and the residue again pyrolyzed at 210–230° for one hour. Distillation and crystallization as above yielded an additional 5.2 g. of anhydride, m. p. 112.5–114°. In a similar run in which the bromine was added rapidly instead of dropwise, the yield of desired product was considerably lowered and skin-irritating by-products were formed.

Reactions of 3-Methylphthalic Anhydride. (a) **Grignard.**—In a typical run, 48 cc. of 1.09 *M* phenylmagnesium bromide in ether was added during fifteen minutes to a well-stirred solution of 8.0 g. of anhydride in 100 cc. of benzene and 60 cc. of ether at room temperature. After refluxing for five hours, the reaction mixture was treated with dilute hydrochloric acid. The total acid fraction weighed 9.1 g. (76.5%) and melted from 94 to 116°. From the neutral portion of the product, 0.54 g. (3.7%) of 2,2-diphenyl-6-methylphthalide III (see below) was isolated.

(b) **Friedel-Crafts.**—In a typical run, 14 g. of aluminum chloride was added to a well-stirred solution of 8.0 g. of anhydride in 125 cc. of benzene at room temperature. Little reaction took place until the mixture was heated, whereupon hydrogen chloride was evolved and a deep red color was produced. After three hours of refluxing the evolution of gas had ceased and the color had faded to yellow. After pouring on ice the acid fraction was isolated as usual and weighed 9.42 g. (80%), m. p. 115–150°. From the neutral fraction was obtained 1.40 g. of III (9.5%).

2,2-Diphenyl-6-methylphthalide, III.—From the neutral fraction of the reaction product obtained by adding 38 cc. of 1.17 *M* phenylmagnesium bromide to 5.30 g. of I in 50 cc. of ether and 50 cc. of benzene and refluxing for sixteen hours, followed by hydrolysis with dilute acid, was isolated 3.50 g. (53%) of III, m. p. 113–115.6°. A sample recrystallized for analysis formed colorless needles, m. p. 114.8–116.0°. When mixed with 3-methylphthalic anhydride there was a large depression of the melting point.

but none when mixed with the phthalide, III, obtained both from Friedel-Crafts and Grignard condensations.

*Anal.*¹⁶ Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.4. Found: C, 83.7; H, 5.0.

Separation of Acid Mixtures into Components.—In a typical separation 9.42 g. of acid mixture, m. p. 115–150° (Friedel-Crafts), was dissolved in 100 cc. of absolute methanol saturated with hydrogen chloride. After refluxing for four hours the alcohol was partly distilled and the cooled solution poured into 150 cc. of water. The product was carefully taken into ether and the unreacted acid recovered by extraction with alkali. The ethereal solution was dried and the ester mixture vacuum distilled. The nearly colorless distillate, 9.3 g., b. p. about 184–187° at 6 mm., was stirred into 50 cc. of concentrated sulfuric acid giving an orange solution. After five minutes this solution was poured into 250 cc. of water whereupon all color vanished. The organic matter was carefully separated into acid and neutral fractions as usual. Crystallization of the acid fraction from benzene yielded 2.90 g. of 2-benzoyl-6-methylbenzoic acid, I, m. p. 123–125°. The neutral fraction was crystallized from a small amount of methanol and yielded 5.04 g. of the normal methyl ester of 2-benzoyl-3-methylbenzoic acid, II, which melted at 102–105°. Upon alkaline hydrolysis this was converted in 94% yield into II, m. p. 172.0–172.9°. The remaining acid had a

(16) Analysis by Mr. D. Mowry.

slightly lower melting point and a wider melting range. The other separations of acid fractions were carried out in the same way and the averaged results are indicated in the Chart. The 36.6% figure in parentheses above formula I in the Chart is the result of taking into account the quantity of III obtained in the Friedel-Crafts reactions. The 44.0% figure below is similarly corrected. As a result of several runs we estimate that the various values may be reproduced to within 5%.

Summary

It is shown that on condensation of 3-methylphthalic anhydride with phenylmagnesium bromide the reaction takes place preferentially at the unhindered carbonyl group, the ratio of 2-benzoyl-6-methylbenzoic acid, I, to 2-benzoyl-3-methylbenzoic acid, II, formed being about 3.5. In the Friedel-Crafts condensation reaction at the two carbonyl groups takes place in approximately equal amounts.

An efficient method for separating mixtures of I and II is described. This method is based on a preferential hydrolysis of the methyl esters of I and II by concentrated sulfuric acid.

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Erythrina Alkaloids. X. Isolation and Characterization of Erysonine and Other Liberated Alkaloids

BY KARL FOLKERS, JOHN SHAVEL, JR., AND FRANK KONIUSZY

β -Erythroidine hydrochloride was given first to dogs¹ and then to humans² for the modification of the severity of the metrazol convulsion, thereby preventing fractures of bones, in the convulsive therapy of the psychoses. The results of Rosen and his co-workers have encouraged our continued study of the alkaloids of hitherto chemically unexamined species of *Erythrina*.

It was shown previously³ that seeds of species of *Erythrina* contain another alkaloidal fraction in addition to the free alkaloidal fraction or the classical combination of the nitrogen bases and organic acids. This new fraction was designated the combined alkaloidal fraction because the nitrogen bases were found to be united with other molecules. This was shown by the fact that the combined molecules in aqueous solution were un-

extractable by the immiscible solvents, and that on acid (preferably) or alkaline hydrolysis, they yielded a solvent soluble fraction, which was designated the liberated alkaloidal fraction. From the liberated bases of eight species of *Erythrina*, four new *Erythrina* alkaloids were isolated: erysodine, erysopine, erysocine and erysovine.⁴

This paper summarizes the pertinent and interesting data resulting from the examination of the liberated alkaloidal fractions obtained from nine additional species of *Erythrina*.⁵

Erysodine and erysopine were isolated again from many of these nine species. One new alkaloid has been isolated from certain samples of *Erythrina costaricensis* Micheli and it has been

(4) The stem "eryso-" was selected for naming the liberated alkaloids, and the stem "erythr-" was used for naming the free alkaloids.

(5) The identity of the *Erythrina* seeds was established by Mr. B. A. Krukoff at the New York Botanical Garden either by determination of accompanying herbarium material or by other evidence which left no doubt regarding the identity.

(1) Rosen, Ziegler and Cominole, *J. Am. Pharm. Assoc.*, **29**, 164 (1940).

(2) Rosen, Cameron and Ziegler, *Psychiatric Quart.*, **14**, 477 (1940).

(3) Folkers and Koniusz, *THIS JOURNAL*, **62**, 1677 (1940).