methyl group of Vb to give α-estradiol, the best yields (10%) were obtained using dihydrophenanthrene as a solvent (390°).

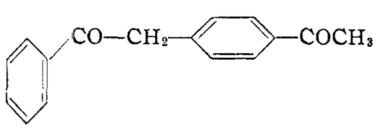
MADISON 6, WISCONSIN RECEIVED JANUARY 26, 1946

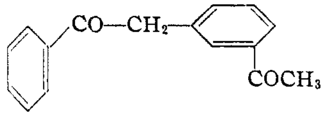
[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF SCHERING CORPORATION]

Anomalous Orientation in a Friedel–Crafts Ketone Synthesis[1]

BY DOMENICK PAPA, ERWIN SCHWENK AND ANNA KLINGSBERG

Although the literature records many instances of m-dialkylbenzene derivatives prepared by Friedel–Crafts alkylation reactions,[2] only one example of m-substitution in a Friedel–Crafts ketone synthesis was found,[3] namely, that desoxybenzoin and acetyl chloride give rise to two isomers.[4]





We have found another example of meta substitution in the Friedel–Crafts reaction of ethyl phenylacetate and acetyl chloride. This reaction was first described by Klewitz[5] and later by Borsche,[4] both of whom apparently obtained only the p-isomer. Our results with this synthesis are at variance with those reported in the literature. Instead of obtaining a uniform, solid ethyl p-acetylphenylacetate, we obtained a mixture of about equal amounts of a liquid and a solid product. This material would not solidify completely, even after prolonged cooling; and, contrary to the literature, did not crystallize uniformly from petroleum ether. On investigation, it was established that in addition to ethyl p-acetylphenylacetate, ethyl m-acetylphenylacetate as well as the corresponding o-derivative resulted from this reaction. While the p- and m-isomers were obtained in about equal yield, only small amounts of the o-compound were found.[6] In view of these results, the reaction between ethyl phenylacetate and chloroacetyl chloride which has been reported[7] to yield the p-isomer exclusively is worthy of note.

While the p-isomer was secured in pure form, it was not possible to free the crude liquid m-isomer from small amounts of both the p- and o-isomers. However, after saponification of the crude m-isomer, pure m-acetylphenylacetic acid was obtained in good yield. The presence of the o-isomer was established by oxidation of the mixture of isomers to the corresponding dicarboxylic acids which gave with resorcinol the characteristic fluorescein test for phthalic acid.

The constitution of the p- and m-isomers (II and III) was established as follows: The ethyl p- and m-acetylphenylacetates after saponification to the free acids (IV and VIII) were oxidized with potassium permanganate to terephthalic and isophthalic acids which were identified as the esters (XIII and XII). Oxidation of IV and VIII with alkali and iodine gave the carboxyphenylacetic acids (V and X). In addition, the esters II and III or the acids IV and VIII were converted to the corresponding phenylene diacetic acids VI and IX by the Willgerodt reaction.

Experimental

All melting points have been corrected for stem exposure. The Friedel–Crafts synthesis is herein described in detail, since Borsche and Sinn[4] give only a brief experimental procedure.

1. **Ethyl Acetylphenylacetate (I).**—In a typical run, 330 g. (2.0 moles) of ethyl phenylacetate was dissolved in three liters of dry carbon disulfide. The mixture was cooled to 0°, and 532 g. (4.0 moles) of finely-powdered anhydrous aluminum chloride[8] was added slowly, with stirring. The temperature was maintained between 0–5° during the addition of the aluminum chloride. To the resulting suspension, at 0°, there was added 250 g. of acetyl chloride in one portion and the reaction mixture stirred for fourteen to sixteen hours at room temperature. The reaction mixture was then placed in a large separatory funnel, the two layers allowed to separate,[9] and the lower layer then slowly added, with stirring, to a mixture of cracked ice and hydrochloric acid. After extraction with ether, the ether extracts were washed with water and dried over sodium sulfate. The solvent was removed under

---

[1] Presented before the Division of Organic Chemistry on April 9, 1946, at the American Chemical Society meeting in Atlantic City.

[2] C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1942.

[3] Recently, in searching for examples of Friedel–Crafts reactions on nitriles, we have encountered an indirect and rather interesting confirmation of our present findings. Kunckell (*Ber.*, **39**, 3145 (1906)) obtained from the Friedel–Crafts reaction of benzyl cyanide and acetyl bromide p-acetyl benzyl cyanide, as well as the m-isomer in unspecified but apparently small yield. He also reported without citing any experimental procedure or evidence that benzyl cyanide and chloroacetyl chloride give rise to two similar isomers. This latter reaction is somewhat surprising in view of his statement that ethyl phenylacetate and chloroacetyl chloride give rise to the ethyl p-chloroacetyl phenylacetate exclusively.—(Added during publication.—*Editor.*)

[4] Borsche and Sinn, *Ann.*, **553**, 261 (1942).

[5] Klewitz, Dissertation, University of Rostock, 1908.

[6] It is of interest to note that in most of the reactions studied by Borsche and others on the use of acetyl and benzoyl chloride with various types of substituted benzene compounds, the non-identified residues, which in certain cases amounted to a considerable percentage of the total yield, have been tentatively designated as other isomers.

[7] Kunckell, *Ber.*, **38**, 2609 (1905).

[8] The aluminum chloride for these experiments was anhydrous, sublimed, reagent grade, manufactured by the General Chemical Company.

[9] The upper layer of carbon disulfide contained 16 g. of ethyl phenylacetate.

anhydrous conditions and the residue esterified by dissolving in 500 cc. of absolute ethyl alcohol and adding slowly, with cooling, 50 cc. of acetyl chloride. After standing overnight, the esterification mixture was poured into two liters of water, extracted with ether and washed with water, dilute sodium carbonate and water. The solvent was removed and the residue fractionated *in vacuo;* yield 240-260 g. (74-80%),[10] b. p. 136-140° (2 mm.). This product was a mixture of solid and liquid which did not solidify completely, even after prolonged cooling.

A typical experimental yield of 250 g., after standing overnight at 0-5°, was filtered and the solid portion washed repeatedly with chilled petroleum ether. The washings were added to the original filtrate and evaporated.

Solid Fraction II.—Yield 100 g., m. p. 60-62°; on recrystallization from petroleum ether, this fraction gave 95 g. of ethyl *p*-acetylphenylacetate melting at 67-68°. Literature m. p. 62-63°; 67-68°. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.68. Found: C, 70.06; H, 7.04.

Liquid Fraction III.—Yield 150 g.; on redistillation, this product boiled at 143-145° (3 mm.). Attempts to further fractionate this material were unsuccessful. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.68. Found: C, 69.93; H, 6.98. The pure ethyl *m*-acetylphenylacetate was obtained by esterifying acid VIII, b. p. 118° (0.5 mm.), $n^{20}D$ 1.5185. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.68. Found: C, 69.66; H, 6.90.

2. ***p*-Acetylphenylacetic Acid** (IV).—To 10 g. of the corresponding ester (II), there was added 100 cc. of 50% sulfuric acid. The mixture was allowed to stand overnight, diluted with water and filtered. After recrystallization from benzene, 8 g. of *p*-acetylphenylacetic acid was obtained as a white crystalline substance melting at 119°. Calcd. for $C_{10}H_{10}O_3$: C, 67.38; H, 5.66; neut. equiv., 179.1. Found: C, 67.28; H, 5.69; neut. equiv., 179.9.

3. **Homoterephthalic Acid** (V).—On oxidizing 0.89 g. of *p*-acetylphenylacetic acid (IV) with iodine and dilute sodium hydroxide[11] there was obtained 0.5 g. of homoterephthalic acid melting at 237-239° after recrystallization from water, literature m. p. 237-238.[12]

4. **Methyl Terephthalate** (XIII).—To 0.72 g. of *p*-acetylphenylacetic acid (IV) was added 4 g. of potassium permanganate in 50 cc. of water plus a few drops of 10% alkali. The oxidation mixture was worked up in the usual manner and the terephthalic acid obtained was converted to the methyl ester. After recrystallization from dilute alcohol, the methylterephthalate melted at 142°, literature 140°.[13]

5. ***p*-Phenylenediacetic Acid** (VI).—*p*-Acetylphenylacetic acid, or its ethyl ester, was converted by the Willgerodt reaction[14] to *p*-phenylenediacetic acid melting at 254-255° after recrystallization from water or aqueous alcohol; literature m. p. 240-241°.[15]

6. **Ethyl *p*-Phenylenediacetate** (VII).—The diester was obtained from acid VI by the usual esterification procedure. On recrystallization from benzene-petroleum ether, the ester melted at 59°, literature 59°.[16]

7. ***m*-Acetylphenylacetic Acid** (VIII).—Cold saponification with dilute sulfuric acid of 20 g. of the liquid fraction yielded 15 g. of *m*-acetylphenylacetic acid melting at 99-104°. After recrystallization from water, 11 g. of pure *m*-acetylphenylacetic acid was obtained melting at 106°. Calcd. for $C_{10}H_{10}O_3$: C, 67.38; H, 5.66; neut. equiv., 178. Found: C, 67.48; H, 5.58; neut. equiv., 177.

8. ***m*-Phenylenediacetic Acid** (IX).—From ethyl *m*-acetylphenylacetate *via* the Willgerodt reaction[14]; m. p. 170° after recrystallization from water; literature m. p. 170°.[17] On esterification, the diester boiled at 145° (1 mm.) and saponification with alkali gave *m*-phenylenediacetic acid of m. p. 170°.

9. **Isohomophthalic Acid** (X).—Oxidation with iodine and alkali as described for the *p*-isomer yielded isohomophthalic acid, which on recrystallization from water melted at 185-187°; literature 184-185°.[18] Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.47; neut. equiv., 90.2. Found: C, 60.24; H, 5.04; neut. equiv., 90.4.

10. **Methyl Isophthalate** (XII).—To 10 g. of the crude liquid ethyl *m*-acetylphenylacetate there was added 75 g. of potassium permanganate in 500 cc. of water. After the oxidation was complete, the reaction mixture was worked up in the usual manner and there was obtained 7 g. of solid acid which did not melt up to 300°. This crude material gave the characteristic fluorescein test for phthalic acid. Five grams of this crude acid was sublimed in a bath at 300-320°. From this sublimation experiment only isophthalic acid was isolated. Upon esterification with methyl alcohol in the usual manner and recrystallization from dilute methanol, the methyl isophthalate melted at 65°, literature m. p. 67-68°.[19]

Summary

1. The Friedel-Crafts reaction between ethyl phenylacetate and acetyl chloride has been shown to give a mixture of isomers, the *p*- and *m*-acetylphenylacetates being obtained in about equal amounts. Small amounts of the *o*-acetyl compound were identified qualitatively.

2. The structure of the two compounds obtained has been established by the preparation of various degradation products.

BLOOMFIELD, N. J. RECEIVED JUNE 25, 1946

---

[10] A forerun of 65-80 g. was obtained which was identified as ethyl phenylacetate, b. p. 78-80° (1 mm.).

[11] Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley & Sons, New York, N. Y., 1940, p. 53.

[12] Komppa, *Ber.*, **68**, 1270 (1935); Mellinghoff, *ibid.*, **22**, 3216 (1889), reports m. p. 285-288°.

[13] Sandmeyer, *Ber.*, **18**, 1498 (1885).

[14] Schwenk and Papa, *J. Org. Chem.*, in press.

[15] Kipping, *Ber.*, **21**, 45 (1888).

[16] Titley, *J. Chem. Soc.*, 2579 (1928).

[17] Kipping, *Ber.*, **21**, 43 (1888).

[18] Komppa and Hirn, *ibid.*, **36**, 3611 (1903).

[19] Baeyer, *ibid.*, **31**, 1404 (1898).