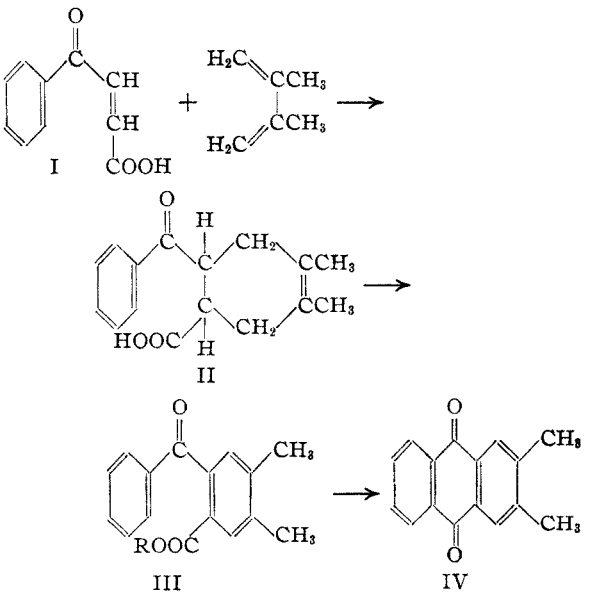
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A New Diene Synthesis of Anthraquinones

BY LOUIS F. FIESER AND MARY FIESER

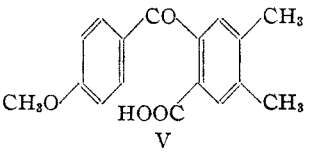
One of the many applications of the Diels–Alder reaction has become the basis of an established method for the synthesis of anthraquinones. The method consists in adding a diene to α-naphthoquinone, or in adding two molecules of a diene to *p*-benzoquinone, and converting the adduct into an anthraquinone by isomerization and oxidation. It occurred to us that another route to members of the anthraquinone series might be developed on the basis of a somewhat different application of the reaction of Diels and Alder.

Aroylacrylic acids such as I are readily available substances, for they can be prepared by the Friedel and Crafts condensation of suitable aromatic substances with maleic anhydride, and by other syntheses. These unsaturated keto acids were found to combine smoothly and practically quantitatively with butadiene or 2,3-dimethylbutadiene in alcoholic solution at 100°, giving adducts of the type of II. Usually only one form of the adduct was observed, but in two cases a small amount of a second stereoisomer was isolated.



As was anticipated, attempts to effect a direct ring closure of the adduct met with little success, and we resorted to dehydrogenation. The dehydrogenation of the free acids proceeded poorly, but by treating the corresponding esters with sulfur it was possible to obtain the pure *o*-benzoylbenzoic esters such as III with an average yield of about 40%. The final step requires no comment.

To test the generality of the synthesis, we used the aroylacrylic acids resulting from the Friedel and Crafts reaction of maleic anhydride with benzene, toluene, *m*-xylene, *p*-xylene, and anisole in combination with the two dienes mentioned above. As was to be expected from the work of Adams and co-workers,[1] difficulty was experienced in effecting the ring closure of the keto acid V (or



V

the ester), for this contains a methoxyl group meta to the position of ring closure. The dimethylmethoxyanthraquinone was obtained in excellent yield, however, by the simple expedient of effecting cyclization through the *o*-benzylbenzoic acid.

Experimental Part[2]

1. The β-Aroylacrylic Acid

The general procedure consisted in adding 0.45 mole of aluminum chloride in one to two hours to a stirred mixture of 0.2 mole of the hydrocarbon (or ether), 0.21 mole of maleic anhydride and 150 cc. of tetrachloroethane, and allowing the reaction to proceed for several hours at room temperature. The yield of the pure reaction product usually was 70–75%, but in the condensations with *m*-xylene and anisole the yield dropped to 41 and 27%, respectively. In these two cases it was necessary to carry out the reaction at 0°. With the one exception noted below, the compounds are all known.

β-(*p*-Xyloyl)-acrylic acid formed fine, yellow needles from ligroin, m. p. 86°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.56; H, 5.93. Found: C, 70.86; H, 5.79.

2. The Diels–Alder Reaction

A mixture of 4 g. of the aroylacrylic acid, 4 cc. of the freshly distilled diene, and 4 cc. of absolute alcohol was heated in a sealed tube in a steam bomb at 100–105° for four to five days. The resulting viscous solution was fil-

(1) Graves and Adams, THIS JOURNAL, **45**, 2439 (1923); Gardner and Adams, *ibid.*, **45**, 2455 (1923); Jacobson and Adams, *ibid.*, **46**, 1312 (1924).

(2) Analyses by Mrs. G. M. Wellwood and by Dr. R. G. Larsen.

tered by suction through a layer of active charcoal, washing out the tube and the charcoal with a liberal quantity of alcohol. Evaporation of the alcohol left an oil which, except in the case of the methoxy compound, partially solidified on being rubbed with petroleum ether. After washing the product on the suction funnel with petroleum ether, about 3 g. of the adduct was obtained as a colorless solid and in a nearly pure condition. The non-crystalline material remaining from the evaporation of the mother liquor consisted largely of the ethyl ester of the adduct, and it was subjected to hydrolysis with alcoholic alkali for two to three hours on the steam-bath. The solution was diluted with water, clarified with animal charcoal, and acidified, when an additional quantity of the free adduct was obtained as a slightly yellow precipitate. One crystallization gave a pure, colorless product with little loss. The addition products are readily soluble in ether and sparingly soluble in petroleum ether, and they crystallize nicely from a combination of these solvents. Except in the case of the methoxy compound, the yield of pure material was 95–98% of the theoretical amount. The adduct from *p*-anisoylacrylic acid did not solidify until the reaction mixture had been subjected to hydrolysis, the crude product was contaminated with a yellow oil, and the yield, pure, was 70%.

The properties and analyses of the adducts are reported in Table I. In the two cases where a higher-melting isomer (probably a stereoisomer) is listed in addition to the main reaction product, this was isolated from the mother liquors of a large scale preparation of the adduct. In the first case 0.2 g. of the isomer was isolated in a 22-g. run; in the second case the yield from 12 g. of starting material was 0.4 g.

3. Dehydrogenation

The methyl esters of the acids listed in Table I appeared to be liquid at room temperature and they were not purified for analysis. Small samples were prepared and dehydrogenated as follows. A solution of 1 g. of the acidic adduct in 10 cc. of methyl alcohol was treated with 1 cc. of concentrated sulfuric acid and refluxed for two hours. The diluted solution was extracted with ether and the ethereal solution was washed with soda solution and dried. The material was transferred to a small distilling flask with a sealed-on receiver, the ether was evaporated and the flask was heated in a nitrate bath at 240–245° to remove traces of solvent. Sulfur (0.24 g.) was added, causing a rapid evolution of gas for about fifteen minutes, and the above bath temperature was maintained for a total of thirty minutes. The material was then distilled in vacuum, giving an oil which partially crystallized. This was washed out with a little ether and by adding petroleum ether the bulk of the product could be obtained as a good solid. This was crystallized from ether–petroleum ether. In those cases where the esters were isolated as solids the yields of pure material varied from 30 to 50%. The properties of these esters are given in Table II.

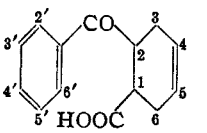
The conditions given above were varied with respect to time, temperature, and amount of sulfur, but with poorer results. Two of the esters were not obtained in a crystalline condition, but in one case hydrolysis of the distilled oil gave a solid keto acid (0.4 g.). The acids are listed in Table III.

4. Ring Closure

Except in the case of the methoxy compound, the anthraquinones were obtained in nearly quantitative yields by heating 0.2 g. of the crystalline keto acid or ester with 2 cc. of concentrated sulfuric acid for one hour on the steam-bath. We were not successful in isolating a crystalline acid or ester in the dehydrogenation of the adduct from butadiene and *p*-toluylacrylic acid, and the oily mixtures on treatment with sulfuric acid gave only a small amount of the anthraquinone, m. p. 169–171°. This was identified as β-methylanthraquinone by comparison with an authentic sample. The other quinones are listed in Table IV.

TABLE I

SUBSTITUTION PRODUCTS OF 1,2,3,6-TETRAHYDRO-2-BENZOYLBENZOIC ACID



Substituents	Form	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4'-Methyl	Small prisms	151.5	73.74	73.82	6.61	6.81
4,5-Dimethyl	Large prisms	143	74.38	74.60	7.03	6.98
Isomer	Long needles	189	74.38	74.40	7.03	7.21
4',4,5-Trimethyl	Large prisms	167.5	74.96	75.26	7.41	7.02
2',4',4,5-Tetramethyl	Prisms	150.5	75.48	75.44	7.75	7.62
Isomer	Needles	165.5	75.48	75.57	7.75	7.90
2',5',4,5-Tetramethyl	Prisms	151	75.48	75.83	7.75	7.81
4'-Methoxy-4,5-dimethyl	Micro plates	149	70.80	70.93	6.99	6.97

TABLE II

DERIVATIVES OF METHYL 2-BENZOYLBENZOATE

Substituents	Form	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4,5-Dimethyl	Micro prisms	123.5	76.09	76.12	6.01	6.29
4',4,5-Trimethyl	Needles	121	76.56	76.67	6.43	6.65
2',4',4,5-Tetramethyl	Prisms	103.5	76.99	76.86	6.81	7.07
2',5',4,5-Tetramethyl	Prisms	110	76.99	77.21	6.81	7.05

TABLE III

DERIVATIVES OF 2-BENZOYLBENZOIC ACID

Substituents	Form	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4,5-Dimethyl	Micro plates	197.5	75.57	75.43	5.55	5.42
4′,4,5-Trimethyl	Micro plates	194.5	76.09	76.16	6.01	6.35
2′,4′,4,5-Tetramethyl	Micro prisms	204.5	76.56	76.32	6.43	6.63
2′,5′,4,5-Tetramethyl	Needles	230	76.56	76.44	6.43	6.41
4′-Methoxy-4,5-dimethyl	Needles	195.5	71.81	71.87	5.68	5.57

TABLE IV

ANTHRAQUINONES

Substituents	Form	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2,3-Dimethyl[a]	Yellow needles	209				
2,3,6-Trimethyl[a]	Yellow needles	233				
2,3,6,8-Tetramethyl	Yellow needles	196	81.78	82.05	6.11	6.36
2,3,5,8-Tetramethyl	Yellow needles	178	81.78	82.20	6.11	6.34
2,3-Dimethyl-6-methoxy	Yellow needles	212	76.67	76.79	5.30	5.62

[a] Found identical with a sample prepared by Fieser and Seligman, THIS JOURNAL, **56**, 2690 (1934).

Like other di-α-substituted anthraquinones, 2,3,5,8-dimethylanthraquinone does not form a vat with alkaline hydrosulfite solution.

4′-Methoxy-4,5-dimethyl-2-benzylbenzoic acid was obtained by heating a mixture of 1.2 g. of 4′-methoxy-4,5-dimethyl-2-benzoylbenzoic acid, 10 g. of zinc dust, 50 cc. of water, and 15 cc. of 25% sodium hydroxide solution (added in portions) for two to three days on the steam-bath; yield, 1 g. The acid forms clusters of small, colorless needles from benzene–ligroin, m. p. 142°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.52; H, 6.71. Found: C, 75.30; H, 6.53.

2,3-Dimethyl-6-methoxyanthrone-10 was obtained in quantitative yield by dissolving the above acid in concentrated sulfuric acid (10 cc. per 0.5 g.) at room temperature, and after two hours pouring the solution onto ice. The anthrone crystallized from alcohol as thin, yellow plates m. p. 151.5°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.40. Found: C, 81.30; H, 6.51.

On heating a solution of the anthrone (0.2 g.) and sodium dichromate (0.17 g.) in glacial acetic acid (5 cc.) on the steam-bath for ten minutes and diluting with water, 0.15 g. of the corresponding quinone (Table IV) was obtained.

Summary

Anthraquinones can be synthesized by adding dienes to aroylacrylic acids, dehydrogenating the adducts in the form of the esters, and cyclizing the *o*-aroylbenzoic esters.

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1′,9-Methylene-1,2,5,6-dibenzanthracene

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In view of the high potency of methylcholanthrene in initiating malignant growth,[1] a knowledge of related compounds is desirable. Using the modified Elbs reaction developed for the synthesis of methylcholanthrene,[2] we have prepared a hydrocarbon having the cholanthrene ring system and one additional aromatic ring.

The starting material was 1-nitroacenaphthene, prepared according to Morgan and Harrison[3] by the nitration of acenaphthene with diacetyl orthonitric acid (22% yield). This was converted into the 1-iodo compound[3] and attempts were made to condense this through the Grignard compound with α-naphthoyl chloride. Like Cook, Haslewood and Robinson,[4] who used 1-iodoacenaphthene in their cholanthrene synthesis, we experienced difficulty in obtaining a satisfactory yield of a condensation product by the usual Grignard technique. We do not agree with these authors that the difficulty is connected with the reluctance of the halide to react with magnesium, for we readily obtained an ethereal solution which was found by titration to contain 90% of the theo-

(1) Cook and Haslewood, *J. Chem. Soc.*, 428 (1934); Barry, Cook, Haslewood, Hewett, Hieger and Kennaway, *Proc. Roy. Soc.* (London), **B117**, 318 (1935).

(2) Fieser and Seligman, THIS JOURNAL, **57**, 228, 942 (1935).

(3) Morgan and Harrison, *J. Soc. Chem. Ind.*, **49**, 413T (1930).

(4) Cook, Haslewood and Robinson, *J. Chem. Soc.*, 667 (1935).