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Synthesis of 7,12-Benz[*a*]anthraquinones via Diels–Alder Reaction of 1,4-Phenanthraquinones

Bruce Irwin Rosen and William P. Weber*

Department of Chemistry, University of Southern California, Los Angeles, California 90007

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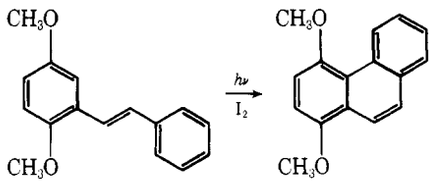
7,12-Benz[*a*]anthraquinones have been prepared by Diels–Alder reaction of 1,4-phenanthraquinones and 1,3-butadiene. The precursors, 1,4-phenanthraquinones, have been prepared in two ways. Photocyclization of 2,5 dimethoxystilbene under oxidizing conditions yields 1,4-dimethoxyphenanthrene, which is demethylated by trimethylsilyl iodide and directly oxidized to 1,4-phenanthraquinone. Diels–Alder reaction of styrenes and 1,4-benzoquinone yields 1,4-phenanthraquinones directly.

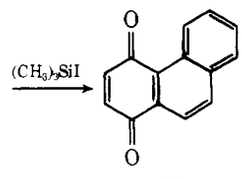
We have been interested in the preparation of substituted 7,12-dimethylbenz[*a*]anthracenes. It should be noted that 7,12-dimethylbenz[*a*]anthracene is one of the most potent carcinogens known.[1,2] 7,12-Dimethylbenz[*a*]anthracene has been prepared efficiently from 7,12-benz[*a*]anthraquinone.[3] Thus a versatile synthesis of substituted 7,12-benz[*a*]anthraquinones would provide a solution to this problem. 7,12-Benz[*a*]anthraquinone has been prepared by direct oxidation of benz[*a*]anthracene.[4] A more general method is the cyclization of *o*-(1-naphthoyl)benzoic acids by treatment with benzoyl chloride and a catalytic amount of sulfuric acid at 140–200 °C.[5-7] The required *o*-(1-naphthoyl)benzoic acids have been prepared by an aluminum chloride catalyzed Friedel–Crafts reaction between phthalic anhydrides and naphthalenes,[7] or by reaction of 1-naphthyl Grignard reagents with phthalic anhydrides.[6] Both methods possess limitations.

By analogy to the successful synthesis of 1,4-naphthoquinone from the Diels–Alder adduct of 1,3-butadiene (I) and 1,4-benzoquinone (II),[8] it appeared to us that the Diels–Alder reaction between 1,3-butadienes and 1,4-phenanthraquinones would provide adducts which could be converted into various 7,12-benz[*a*]anthraquinones. However, examination of the chemical literature revealed not a single example of a Diels–Alder reaction involving 1,4-phenanthraquinone (III). This is probably due to the fact that while III has been known for almost 50 years, its preparation by classical methods is difficult.[9,10] We should like to report two new methods to prepare III and the first example of its Diels–Alder reactivity.

Our first approach was based on the photochemical cyclization of stilbenes to phenanthrene derivatives under oxidizing conditions.[11-13] Thus, we have found that photolysis of a dilute solution of 2,5-dimethoxystilbene (IV)[14] in the presence of iodine with a 450-W medium-pressure Hanovia Hg lamp leads to production of 1,4-dimethoxyphenanthrene in 71% yield. The direct oxidation of this hydroquinone dimethyl ether with argentic oxide to III failed.[15] An alternative plan called for demethylation of 1,4-dimethoxyphenanthrene to the corresponding 1,4-dihydroxyphenanthrene, which could be oxidized to yield III. Demethylation, however, proved to be no trivial task. Among the demethylation procedures which failed were the use of LiI in collidine[16] and sodium ethyl thiolate in DMF.[17,18] Fortunately, trimethylsilyl iodide[19] proved a successful demethylating reagent.[20] Further, 1,4-dihydroxyphenanthrene must be easily oxidized, since under the reaction conditions (air was not rigorously excluded) the product isolated was III. Problems associated with this



IV



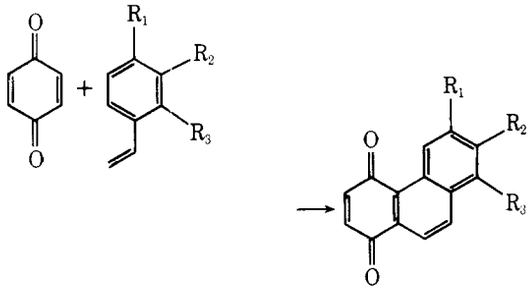
III

method are that quite dilute solutions of IV must be used (≃1 g/L) and relative long photolysis times. Further, neither IV (prepared from 2,5-dimethoxybenzaldehyde by a Wittig reaction) nor trimethylsilyl iodide are commercially available. Nevertheless, by comparison to previous methods this procedure provides a practical approach to 1,4-phenanthraquinones.

Our second systhesis of III is even more direct and over-

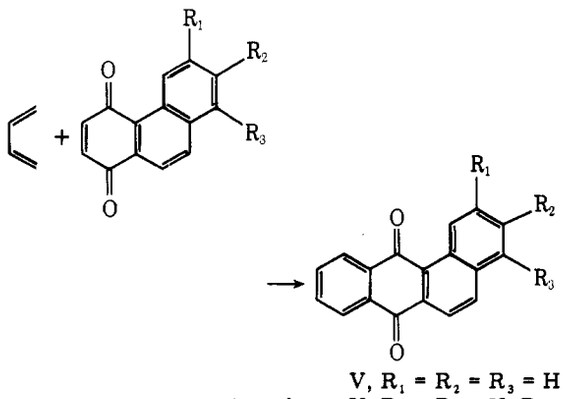
comes most of the limitations discussed above. Styrene is not usually thought of as a potential 1,3-diene system for Diels–Alder reactions; however, a limited number of such reactions have been reported.[21,22]

Thus, the direct Diels–Alder reaction of II with styrene should yield a tetrahydro adduct capable of facile oxidation to III. Examination of the literature reveals at least two reports of success with this type of Diels–Alder reaction.[23,24] Thus reaction of methoxy-II with styrene is reported to yield 3-methoxy-III.[24] On the other hand, reaction of styrene with II is reported to yield a 2:1 styrene/II adduct.[25] We find that heating dilute solutions of styrene and II in xylene at reflux leads to a 30% yield of III. Apparently the initial tetrahydro adduct is dehydrogenated under the reaction conditions, possibly by excess II, to yield III directly. Analogous reactions with *o*-,[26] *m*-,[27] *p*-,[27] and 3,4-dimethoxystyrene[27] led respectively to 8-methoxy-III, 7-methoxy-III, 6-methoxy-III, and 6,7-dimethoxy-III in 20–30% yields. It should be noted that *m*-methoxystyrene might be expected to react with II to yield two products: 7-methoxy-III and 5-methoxy-III. No 5-methoxy-III was detected. This is probably due to the well-known steric hindrance between the C-4 and C-5 positions in phenanthrenes. This is a limitation to the generality of this method.



III, $R_1 = R_2 = R_3 = H$
8-methoxy-III, $R_1 = R_2 = H$; $R_3 = OCH_3$
7-methoxy-III, $R_1 = R_3 = H$; $R_2 = OCH_3$
6-methoxy-III, $R_2 = R_3 = H$; $R_1 = OCH_3$
6,7-dimethoxy-III, $R_3 = H$; $R_1 = R_2 = OCH_3$

III smoothly underwent a Diels–Alder reaction with I under pressure at 90 °C to yield directly 7,12-benz[*a*]anthraquinone (V) in 90% yield. Apparently the initial tetrahydro adduct is easily oxidized on workup in air to yield V. Analogous reaction with 8-methoxy-III, 7-methoxy-III, 6-methoxy-III, and 6,7-dimethoxy-III led respectively to 4-methoxy-V, 3-methoxy-V, 2-methoxy-V, and 2,3-dimethoxy-V in 75–90% yields.



V, $R_1 = R_2 = R_3 = H$
4-methoxy-V, $R_1 = R_2 = H$; $R_3 = OCH_3$
3-methoxy-V, $R_1 = R_3 = H$; $R_2 = OCH_3$
2-methoxy-V, $R_2 = R_3 = H$; $R_1 = OCH_3$
2,3-dimethoxy-V, $R_3 = H$; $R_1 = R_2 = OCH_3$

Experimental Section

The National Cancer Institutes Safety Standards for Research Involving Chemical Carcinogens were followed.

IR spectra were determined with KBr pellets on a Beckman Acculab 2 spectrometer and were calibrated against known bands in a polystyrene film. NMR spectra were recorded on a Varian XL-100 spectrometer, using 10% solutions in $CDCl_3$ with an internal standard of Me_4Si. Ultraviolet spectra were obtained in 95% ethanol on a Beckman Acta M spectrometer. Melting points were taken on a Hoover-Thomas apparatus and are uncorrected. High resolution mass spectra were run at the California Institute of Technology Microanalytical Laboratory, Pasadena, Calif., on a DuPont 21-492 mass spectrometer.

Preparation of 1,4-Dimethoxyphenanthrene. A mixture of 1.0 g (4.15 mmol) of IV[14] and two crystals of iodine was dissolved in 700 mL of olefin-free hexane. This solution was photolyzed using a 450-W medium-pressure Hanovia lamp. The reaction mixture was then evaporated to dryness under reduced pressure. The crude product was dissolved in 20 mL of hexane, poured into a 2.5 × 10 cm column of alumina, and eluted with hexane/1% EtOAc followed by TLC. The eluent was evaporated to yield 0.70 g (71%) of 1,4-dimethoxyphenanthrene as white crystals, mp 118.5 °C: NMR δ 9.1 (m, 1 *H*), 8.2 (d, 1 H, *J* = 9 Hz), 7.8 (m, 2 H), 7.6 (m, 2 H), 6.95 (dd, 2 H, *J* = 12 and 9 Hz), 4.0 (s, 3 H), 3.9 (s, 3 H); IR C=C 1610 cm^{-1}; UV 2471 Å (ε 1.41 × 10^4), 2660 (1.07 × 10^4), 2790 (1.29 × 10^4), 3025 (6.7 × 10^3), 3140 (5.65 × 10^3), 3315 (2.34 × 10^3), 3480 (3.57 × 10^3), 3650 (3.84 × 10^3). Calcd for $C_{16}H_{14}O_2$, parent ion *m/e* 238.101; found 238.102.

Preparation of III. Method A: Oxidative Demethylation of 1,4-Dimethoxyphenanthrene. In a three-neck, 100-mL, round-bottom flask equipped with a Teflon stirring bar and a condenser was placed 35 mL of CCl_4, 0.22 g (0.925 mmol) of 1,4-dimethoxyphenanthrene, and excess $(CH_3)_3SiI$.[19,20] The reaction was refluxed for 48 h under an atmosphere of N_2 and then quenched with H_2O. The organic fraction was separated, dried ($MgSO_4$), filtered, and evaporated. The crude product was dissolved in 20 mL of hexane and poured into a 2.5 × 10 cm column of alumina and eluted with 5% EtOAc/hexane; the major fraction (yellow band) was collected and evaporated to yield 0.15 g (78%) of III as yellow crystals, mp 145 °C (lit. mp 148 °C):[8,9] NMR δ 9.5 (dd, 1 H, *J* = 9 and 2 Hz), 8.1 (s, 2 H), 7.9–7.5 (m, 3 H), 6.85 (s, 2 H); IR C=O 1670 cm^{-1}, 1660, C=C 1620; UV data was in agreement with literature.[9]

Preparation of III. Method B: Diels–Alder Reaction of Styrene and II. In a three-neck, 500-mL, round-bottom flask equipped with a pressure-equalizing addition funnel, a condenser, and a Teflon stirring bar was placed 5 g (50 mmol) of II in 250 mL of xylene. The solution was heated to reflux and to it was added dropwise over 5 h 4.9 g (47 mmol) of styrene. The solution was refluxed overnight. After cooling, the solvent was evaporated under reduced pressure. The crude product was dissolved in 10 mL of 5% EtOAc/hexane, poured into a 2.5 × 10 cm column of alumina, and eluted with 5% EtOAc/hexane; the major fraction (yellow band) was collected and evaporated to yield 1.4 g (14.3%) of III. Its properties were identical with those of samples prepared by method A.

6-Methoxy-III was prepared as above by the reaction of 2.0 g (15 mmol of *p*-methoxystyrene[27] and 2.8 g (26 mmol) of II to yield 1.1 g (31%) of 6-methoxy-III (orange crystals), mp 195 °C: NMR δ 9.0 (d, 1 H, *J* = 2 Hz), 8.01 (dd, 2 H, *J* = 12 and 8 hz), 7.75 (d, 1 H, *J* = 10 Hz), 7.3 (d, 1 H, *J* = 2 Hz), 6.9 (s, 2 H), 3.98 (s, 3 H); IR C=O 1655 cm^{-1}, C=C 1620; UV 2315 Å (ε 5.26 × 10^4), 2700 (1.60 × 10^4), 2900 (1.3 × 10^4), 3880 (4.96 × 10^3). Calcd for $C_{15}H_{10}O_3$, parent ion *m/e* 238.063; found 238.065.

7-Methoxy-III was prepared as above by the reaction of 2.5 g (19 mmol) of *m*-methoxystyrene[27] and 4.5 g (42 mmol) of II to yield 0.85 g (19%) of 7-methoxy-III (orange crystals), mp 140 °C: NMR δ 9.35 (d, 1 H, *J* = 10 Hz), 8.95 (dd, 2 H, *J* = 13 and 8 Hz), 7.25 (dd, 1 H, *J* = 10 and 4 Hz), 7.0 (d, 1 H, *J* = 4 Hz), 6.78 (s, 2 H), 3.76 (s, 3 H); IR C=O 1660 cm^{-1}, C=C 1620; UV 2334 Å (ε 3.53 × 10^4), 2600 (1.09 × 10^4), 2940 (1.04 × 10^4), 3023 (1.07 × 10^4). Calcd for $C_{15}H_{10}O_3$, parent ion *m/e* 238.063; found 238.062.

8-Methoxy-III was prepared as above by the reaction of 2.1 g (16 mmol) of *o*-methoxystyrene[26] and 4.3 g (40 mmol) of II to yield 1.15 g (30%) of 8-methoxy-III (dark red-brown crystals), mp 204 °C: NMR δ 9.05 (d, 1 H, *J* = 9 Hz), 8.65 (d, 1 H, *J* = 8 Hz), 8.1 (d, 1 H, *J* = 8 Hz), 7.58 (t, 1 H, *J* = 8 Hz), 6.9 (br s, 3 H), 3.98 (s, 3 H); IR C=O 1660 cm^{-1}, C=C 1615; UV 2210 Å (ε 2.46 × 10^4), 2584 (7.75 × 10^3), 3001 (1.03 × 10^4), 3679 (1.65 × 10^3). Calcd for $C_{15}H_{10}O_3$, parent ion *m/e* 238.063; found 238.065.

6,7-Dimethoxy-III was prepared as above by the reaction of 2.0 g (12.2 mmol) of 3,4-dimethoxystyrene[27] with 3.2 g (29 mmol) of II to yield 0.7 g (21%) of 6,7-dimethoxy-III (orange crystals), mp 236 °C dec: NMR δ 9.0 (s, 1 H), 7.0 (s, 2 H), 7.02 (s, 1 H), 6.82 (s, 2 H), 4.0 (s, 3 H), 3.96 (s, 3 H); IR C=O 1670 cm^{-1}, 1650, C=C 1620; UV 2450 Å (ε 8.25 × 10^4), 2900 (1.48 × 10^4), 3020 (1.01 × 10^4), 4273 (9.07 × 10^3).

Calcd for $C_{16}H_{12}O_4$, parent ion *m/e* 268.073; found 268.071.

Preparation of V. Into a pressure bottle was placed 0.09 g (0.43 mmol of III, 25 mL of benzene, and a Teflon stirring bar. The solution was cooled to −78 °C and excess I was condensed in. The bottle was capped and the reaction flask was heated to 90 °C and stirred overnight. The flask was then cooled and vented and the solvent was removed under reduced pressure. The crude product was dissolved in 5 mL of hexane and poured into a column of alumina. Elution with hexane removed butadiene polymer. This was followed by elution with 15% EtOAc/hexane to move the desired product from the column. The eluent was evaporated to yield 0.10 g (90%) of V (greenish crystals), whose spectral (UV, NMR) properties were identical with those of an authentic sample (Aldrich), mp 165–166 °C (lit. mp 166–167 °C).[4]

2-Methoxy-V was prepared as above by the reaction of 0.10 g (0.42 mmol) of 6-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.11 g (91%) of V (yellow crystals), mp 195 °C (lit. mp 200 °C):[28] NMR δ 9.2 (d, 1 H, J = 4 Hz), 8.3–8.0 (m, 4 H), 7.8–7.65 (m, 3 H), 7.3 (d, 1 H, J = 4 Hz), 4.0 (s, 3 H); IR C=O 1670 cm^{-1}, C=C 1625; UV 2236 Å (ε 1.93 × 10^4), 2555 (1.71 × 10^4), 2903 (9.5 × 10^3), 3010 (8.25 × 10^3), 4408 (1.69 × 10^3).

3-Methoxy-V was prepared as above by the reaction of 0.05 g (0.21 mmol) of 7-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.045 g (75%) of 3-methoxy-V (yellow crystals), mp 145 °C: NMR δ 9.5 (d, 1 H, J = 10 Hz), 8.3–7.9 (m, 4 h), 7.75–7.6 (m, 2 H), 7.3 (dd, 1 H, J = 10 and 3 Hz), 7.1 (d, 1 H, J = 3 Hz), 3.9 (s, 3 H); IR C=O 1670 cm^{-1}, C=C 1620; UV 2241 Å (ε 3.22 × 10^4), 2456 (2.13 × 10^4), 2530 (1.99 × 10^4), 3037 (2.95 × 10^4), 3841 (4.02 × 10^3). Calcd for $C_{19}H_{12}O_3$, parent ion *m/e* 288.079; found 288.076.

4-Methoxy-V was prepared as above by the reaction of 0.025 g (0.11 mmol) of 8-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.026 g (88%) of 4-methoxy-IV (red-orange crystals), mp 212 °C (lit. mp 220 °C):[29] NMR δ 9.22 (d, 1 H, J = 10 Hz), 8.7 (d, 1 H, J = 10 Hz), 8.3–8.18 (m, 3 H), 7.8–7.5 (m, 3 H), 6.9 (d, 1 H, J = 8 Hz), 3.98 (s, 3 H); IR C=O 1670 cm^{-1}, C=C 1590; UV 2184 Å (ε 2.71 × 10^4), 2461 (1.32 × 10^4) 2800 (8.69 × 10^3), 3007 (1.51 × 10^4), 4322 (1.22 × 10^3).

2,3-Dimethoxy-V was prepared as above by the reaction of 0.116 g (0.43 mmol) of 6,7-dimethoxy-III and excess 9.7 g (200 mmol) of I to yield 0.11 g (80%) of 2,3-dimethoxy-V (yellow crystals), mp 237 °C dec: NMR δ 9.2 (s, 1 H), 8.3–8.1 (m, 3 H), 7.94 (d, 1 H, J = 9 Hz), 7.8–7.65 (m, 2 H), 7.08 (s, 1 H), 4.1 (s, 3 H), 4.0 (s, 3 H); IR C=O 1660 cm^{-1}, 1650, C=C 1620; UV 2250 Å (ε 1.71 × 10^4), 2450 (1.11 × 10^4), 2571 (9.3 × 10^3), 2902 (5.9 × 10^3), 3025 (5.9 × 10^3), 3290 (2.27 × 10^3), 4225 (2.41 × 10^3). Calcd for $C_{20}H_{14}O_4$, parent ion *m/e* 318.089; found 318.087.

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Registry No.—I, 106-99-0; II, 106-51-4; III, 569-15-3; 6-methoxy-III, 63216-06-8; 7-methoxy-III, 63216-07-9; 8-methoxy-III, 63216-08-0; 6,7-dimethoxy-III, 63216-09-1; IV, 21889-09-8; 2-methoxy-V, 63216-10-4; 3-methoxy-V, 63216-11-5; 4-methoxy-V, 16277-48-8; 23-dimethoxy-V, 63216-12-6, 1,4-dimethoxyphenanthrene, 63216-13-7; *p*-methoxystyrene, 637-69-4; *m*-methoxystyrene, 626-20-0; *o*-methoxystyrene, 612-15-7; 3,4-dimethoxystyrene, 17055-36-6; styrene, 100-42-5.

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A General Synthesis of 1-, 2-, 3-, and 4-Substituted Benz[a]anthracene-7,12-diones

Wayne B. Manning,* Joseph E. Tomaszewski, Gary M. Muschik, and Ronald I. Sato

Chemical Carcinogenesis Program, NCI–Frederick Cancer Research Center, Frederick, Maryland 21701

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Various 1-, 2-, 3-, and 4-substituted derivatives of benz[a]anthracene-7,12-dione (4) have been prepared by reaction of ring-substituted styrenes and 1,4-naphthoquinone (5) in the presence of chloranil. Comparative reactions done with and without chloranil demonstrated that chloranil had a positive effect upon the yield of the substituted benz[a]anthracene-7,12-diones. The preparation of 1,4-dimethylbenz[a]anthracene-7,12-dione in yields comparable with those obtained for the monosubstituted diones demonstrated that certain steric problems of the Diels–Alder reaction could be overcome. Spectral data are discussed.

The current interest in the metabolites of benz[a]anthracene and 7,12-dimethylbenz[a]anthracene as potential carcinogens has prompted study into synthetic methods to prepare these compounds. Recent preparations of substituted benz[a]anthracenes and 7,12-dimethylbenz[a]anthracenes (DMBAs) have been based upon multistep syntheses using substituted naphthalenes and phthalic anhydrides in a Friedel–Crafts acylation, followed by cyclization of the re-