Heterocyclic Quinones. 1-Azaanthraquinones and 4-Azaphenanthraquinones[1]

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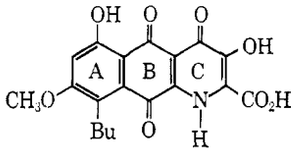
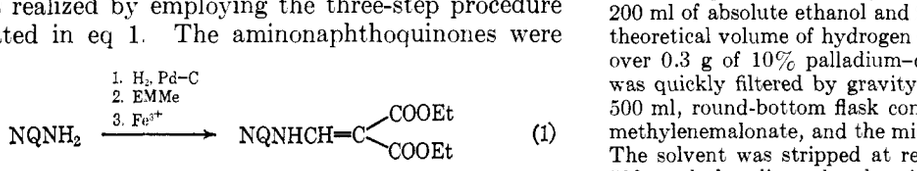
Phomazarin, the unique 1-azaanthraquinone metabolite of *Phoma terrestris* Hansen, was isolated over a score of years ago by Kögl and co-workers. While degradative,[4] biosynthetic,[5] and recent spectral studies[6] have aided in the arrangement of constituents in the heterocyclic ring of phomazarin[7] (*e.g.*, **1**, ring C), suitable models of the 1-azaanthraquinone system have not been available to permit a comparison of properties with those exhibited by the metabolite and its derivatives. In this connection, we sought a method of preparation for the 1-azaanthraquinone system and report here the results of a brief investigation on a variant of the Conrad–Limpach and Knorr syntheses.[8]

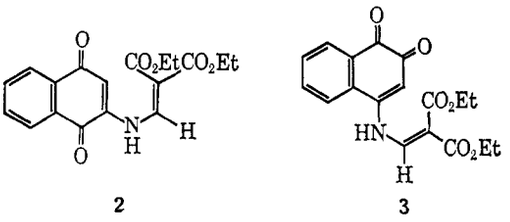


1

The reaction of either 2-amino-1,4-naphthoquinone or 4-amino-1,2-naphthoquinone with diethyl ethoxymethylenemalonate (EMME) was found inadequate for the preparation of naphthoquinonylaminomethylenemalonates (*e.g.*, **2** and **3**), presumably because of the "amide-like" character of the 2- and 4-amino groups of the naphthoquinone.[9] A synthesis for compounds **2** and **3** was realized by employing the three-step procedure indicated in eq 1. The aminonaphthoquinones were converted by hydrogenation over palladium on charcoal to the more basic aminonaphthohydroquinones and, without taking precaution to prevent aerobic oxidation, the solutions were quickly filtered free of catalyst, treated with EMME, and heated under reflux for 2–3 hr. Evaporation of the deeply colored reaction solutions provided residues of apparent quinhydrone nature, which upon solution in chloroform and oxidation by iron(III) solution gave the desired compounds **2** and **3**.

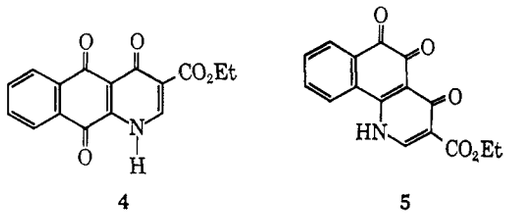


(1)



2 **3**

In refluxing Dowtherm A,[10] the naphthoquinonylaminomethylenemalonates **2** and **3** cyclized[8b] to the 1-azaanthraquinone (**4**) and the 4-azaphenanthraquinone (**5**), respectively. The nuclear magnetic resonance (nmr) spectra of the ring-closed products were in agreement with the foregoing assignments, inasmuch as resonances characteristic of quinonoidal protons were not observed.



4 **5**

Experimental Section[11]

Diethyl 2-(1,4-Naphthoquinonyl)aminomethylenemalonate (2).—The suspension of 5.0 g of 2-amino-1,4-naphthoquinone[12] in 200 ml of absolute ethanol and 20 ml of acetic acid absorbed the theoretical volume of hydrogen (712 ml) at atmospheric pressure over 0.3 g of 10% palladium–charcoal. The colorless solution was quickly filtered by gravity (orange color developed) into a 500 ml, round-bottom flask containing 15 ml of diethyl ethoxymethylenemalonate, and the mixture was refluxed for 2.5–3.0 hr. The solvent was stripped at reduced pressure (2–5 mm) below 50°, and the olive-colored residue was digested with 50 ml of hot benzene for 15–20 min. The insoluble olive product was washed with petroleum ether (bp 30–60°): yield 6.0–7.2 g.

The crude quinhydrone (6.0 g) in 40 ml of ethanol and 300 ml of chloroform was shaken vigorously with a solution of 16.2 g of $FeCl_3 \cdot 6H_2O$ in 25 ml of concentrated hydrochloric acid and

(1) (a) The compounds reported within this paper have been resynthesized and submitted to the U. S. Army Medical Research and Development Command for evaluation of antimalarial activity under Contract No. DA-49-193-MD-2862 to the Research Triangle Institute, Research Triangle Park, N. C. This paper is contribution number 180 from the Army Research Program on Malaria. (b) The 1-azaanthraquinones and 4-azaphenanthraquinones are derivatives of the benzo[*g*]quinoline and benzo[*h*]quinoline systems, respectively.

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(4) (a) F. Kögl and J. Sparenburg, *Rec. Trav. Chim.*, **59**, 1180 (1940); (b) F. Kögl and F. W. Quackenbush, *ibid.*, **63**, 251 (1944); (c) F. Kögl, G. C. Van Wessem, and O. I. Elsbach, *ibid.*, **64**, 23 (1945).

(5) A. J. Birch, R. I. Fryer, P. J. Thomson, and H. Smith, *Nature*, **190**, 441 (1961).

(6) A. J. Birch, D. N. Butler, and R. W. Rickards, *Tetrahedron Letters*, No. 28, 1853 (1964).

(7) Since the completion of this work, the structure of phomazarin has been revised with regard to the placement of the constituents in the heterocyclic ring (*cf.* ref 6).

(8) (a) N. Campbell, in "Chemistry of Carbon Compounds," E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1957, Vol. IVa, p 590. (b) C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.*, **68**, 1204 (1946); C. C. Price, N. J. Leonard, and H. F. Herbrandson, *ibid.*, **68**, 1251 (1946).

(9) L. F. and M. Fieser, *ibid.*, **56**, 1565 (1934).

(10) Dowtherm A, bp ~495° F, is a heat-transfer medium containing a mixture of 26.5% diphenyl and 73.5% diphenyl oxide by weight. It is produced commercially by The Dow Chemical Co., Midland, Mich.

(11) Thin layer plates were prepared by coating microscope slides with silica gel H. The following abbreviations represent the solvent systems employed for the elution of chromatograms: A, benzene–ethyl acetate–acetic acid (90:10:1); B, benzene–ethyl acetate–acetic acid (9:1:1); C, the organic phase of 1-butanol-pyridine–saturated sodium chloride solution (1:1:2); and D, the organic phase of acetic acid–1-butanol–water (6:25:25). Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Ultraviolet and visible spectra were measured on a Cary Model 14 spectrophotometer. Nmr spectra (in parts per million) were recorded on a Varian A-60 and, unless otherwise noted, using trifluoroacetic acid as solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer; samples were prepared in the form of pressed potassium bromide disks. Microanalyses were carried out by one of us (K. H. D.) and Micro-Tech Laboratories, Skokie, Ill.

(12) L. F. Fieser and J. L. Hartwell, *ibid.*, **57**, 1482 (1935).

500 ml of water for 3–5 min. The organic phase was washed with 200 ml of water, dried (sodium sulfate), and evaporated at reduced pressure. The orange residue was best recrystallized using the following procedure. The solid was dissolved by gentle warming in a mixture of 25 ml of absolute ethanol and 150 ml of toluene, and the resulting solution allowed to attain room temperature. Seven 20-ml portions of petroleum ether (bp 30–60°) were successively added with good mixing after each addition, and then the mixture kept 1 hr at room temperature, during which a crop of bright orange needles separated. Another 100-ml portion of petroleum ether was added, and the product was collected after another hour, washed with petroleum ether, and vacuum dried: yield 3.90 g; melting and resolidifying at 142°, followed by sharp melting at 151.5–152.5°. A second crop (1.05 g, mp 148–153°) was obtained by adding 300 ml of petroleum ether to the mother liquor and allowing the solution to stand at ~6°. Both crops were chromatographically uniform in solvent system A. The combined yield was 4.95 g (50%): infrared, 1700, 1685, 1650, and 1590 cm^{-1}; ultraviolet, λ_{max}^{MeOH} 258 mμ ($\epsilon \times 10^{-3} = 12.6$), 299 (27.4), 422 (9.75); nmr (trifluoroacetic acid solution containing 1 drop of deuterium oxide), δ 8.40 (singlet, 0.94 proton, NHC*H*=C<), 6.72 (singlet, 1.05 protons, quinone ring proton).

Anal. Calcd for $C_{18}H_{17}NO_6$ (343.3): C, 62.97; H, 4.99; N, 4.08. Found: C, 63.19; H, 5.05; N, 4.15.

Diethyl 4-(1,2-Naphthoquinonyl)aminomethylenemalonate (3).—A suspension of 5.0 g of 4-amino-1,2-naphthoquinone[12] was reduced and allowed to react with diethyl ethoxymethylenemalonate as described under the procedure for **2**. Evaporation of the reaction solution gave a crude quinhydrone, which without further manipulation was dissolved in a mixture of ethanol and chloroform. After the usual treatment with iron(III) solution, washing, and evaporation of the dried organic solution, the crude naphthoquinone **3** was isolated as an orange-brown crystalline solid. This solid was digested with 50 ml of ethanol, filtered, and washed with ether: yield 6.0 g (chromatographically impure, two zones). The product was recrystallized from approximately 1 l. of absolute ethanol (preheated to boiling before adding compound) to give 4.83 g (49%) of metallic-lustered orange platelets: mp 176–189° dec; the compound moved as one zone in solvent systems A and B; infrared, 1725, 1695, 1655 sh, 1643, 1625, and 1590 cm^{-1}; ultraviolet, λ_{max}^{MeOH} 255 mμ ($\epsilon \times 10^{-3} = 19.9$), 297 (12.0), 333 (12.8), 438 (7.60); λ_{sh}^{MeOH} 342 (12.5); nmr, δ 8.73 (singlet, 1.03 protons, NHC*H*=C<), 6.97 (singlet, 1.03 protons, quinone ring proton).

Anal. Calcd for $C_{18}H_{17}NO_6$ (343.4): C, 62.97; H, 4.99; N, 4.08. Found: C, 63.00; H, 5.00; N, 4.42.

3-Carboethoxybenzo[*g*]quinoline-4,5,10-trione (4).—A solution of 3.15 g of **2** in 50 ml of Dowtherm A was heated under reflux for 45 min and then kept at room temperature for 2 hr. The light yellow, crystalline product was filtered and washed with a little Dowtherm and then thoroughly with petroleum ether. After vacuum drying overnight, the product (2.1 g) still gave a strong diphenylether odor. The material was recrystallized from approximately 90 ml of toluene (activated charcoal) to give 1.37 g (50%), mp 226–228.5°, of soft yellow needles. The compound moved as one zone (tlc) when chromatograms were eluted with solvent systems A, C, and D. The compound crystallized from absolute ethanol as small yellow prisms: mp 224–226.5°; infrared, 1720, 1680, 1630, and 1580 cm^{-1}; ultraviolet, λ_{max}^{MeOH} 250 mμ ($\epsilon \times 10^{-3} = 23.2$), 320 (4.93), 390 (2.60); λ_{sh}^{MeOH} 260 (20.9), 274 (14.4), 280 (10.3); $\lambda_{max}^{6\ N\ HCl}$ 240 (24.0), 265 (22.5), 307 (5.25), 352 (4.15); $\lambda_{max}^{0.1\ N\ NaOH}$ 225 (24.6), 247 (28.6), 252 (28.2), 272 (18.7), 330 (3.62), 425 (4.80); nmr, δ 9.54 (singlet, 1.00 proton, heterocyclic ring proton).

Anal. Calcd for $C_{16}H_{11}NO_5$ (297.3): C, 64.65; H, 3.73; N, 4.71. Found: C, 64.86; H, 4.04; N, 4.81.

3-Carboethoxybenzo[*h*]quinoline-4,5,6-trione (5).—A solution of 3.0 g of **3** in 20 ml of Dowtherm A was heated under reflux for 45 min and then kept at room temperature for 4–5 hr. The crop of heavy, dark brown crystals (2.3 g) was collected, washed successively with Dowtherm and petroleum ether, and recrystallized from 60 ml of toluene (activated charcoal) to give golden brown crystals (1.7 g), mp 233–237° with a crystalline change occurring at ~185°. One further recrystallization using 40 ml of toluene (activated charcoal) gave 1.3 g of metallic-lustered gold plates, which melted and resolidified in the form of needles at 183–186°. The latter crystalline form then melted at 233–235°: the compound moved as one zone (tlc) in solvent systems A and B; infrared, 1715, 1690, 1630 and 1580 cm^{-1}; ultraviolet, λ_{max}^{MeOH} 261 mμ ($\epsilon \times 10^{-3} = 30.9$), 325 (4.42); λ_{sh}^{MeOH} 245 (22.0), 350 (3.62); $\lambda_{max}^{6\ N\ HCl}$ 278 (28.7), 363 (5.14); $\lambda_{sh}^{6\ N\ HCl}$ 320 (5.46); $\lambda_{max}^{0.1\ N\ NaOH}$ 254 (32.5), 328 (4.25), 430 (4.62); $\lambda_{sh}^{0.1\ N\ NaOH}$ 245 (28.2); nmr, δ 9.45 (singlet, 1.04 protons, heterocyclic ring proton).

Anal. Calcd for $C_{16}H_{11}NO_5$ (297.3): C, 64.65; H, 3.73; N, 4.71. Found: C, 64.65; H, 3.72; N, 4.91.

Quinoxaline Derivative of 5.—To a suspension of 100 mg of **5** in 5.0 ml of acetic acid was added a solution of 100 mg of *o*-phenylenediamine in 5.0 ml of acetic acid. After 15 min, the original suspension of **5** had passed to one consisting of a spongy, light yellow solid. The mixture was warmed until a clear solution had formed and then set aside until the contents formed a solid mass. The light yellow product (110 mg) was filtered and washed successively with acetic acid, ethanol, and ether. When recrystallized from approximately 5 ml of acetic acid, the derivative, mp 176°, had no definite crystalline form when examined under the microscope. The compound crystallized from absolute ethanol as canary yellow, microcrystalline needles: mp 178–179.5°; it moved as one zone in solvent systems A and B; ultraviolet, λ_{max}^{EtOH} 261 mμ ($\epsilon \times 10^{-3} = 77.0$), 381 (18.2), 402 (22.4).

Anal. Calcd for $C_{22}H_{15}N_3O_3$ (369.4): C, 71.53; H, 4.09; N, 11.38. Found: C, 71.28; H, 4.12; N, 11.56.

Some Properties of Compounds 2–5.—Aside from the fact that only **5** would form a quinoxaline derivative and the observation that the color of **4** in aqueous solution was completely bleached at moderate acid strength (10^{-4} to 10^{-5} *M* solutions in 6 *N* hydrochloric acid), the tricyclic azaquinones **4** and **5** exhibited some common properties, which in the past have been used qualitatively for differentiating between *o*- and *p*-quinones. Both **4** and **5** reacted with cold, saturated bisulfite solution[13] to give insoluble white precipitates and, in tests conducted by suspending a few crystals in the cold solution and allowing the suspension to stand at ~6°, the 1-azaanthraquinone **4** was observed to react more rapidly. Contrasting with the striking color differences of comparable heterocyclic *o*- and *p*-quinones,[14] the azaquinones **4** and **5** exhibited similar colors; in fact, the similarity in color allows aged or impure samples of **4** to be easily mistaken for **5**.

When *Phoma terrestris* Hansen was grown on a Czapek-Dox medium containing starch,[4a] the dark violet color contained on the underside of the mycelium was attributed to the presence of a sodium or potassium salt of the phomazarin. In this connection, we have tested the colors imparted to 0.1 *N* sodium hydroxide solution by the compounds prepared in this study. When relatively concentrated solutions of the azaquinones **4** and **5** in alcohol were treated with a few drops of 1% sodium hydroxide solution, neither a permanent nor transient violet color was imparted to the solution; alkaline solutions of **4** and **5** were yellow and yellow-orange, respectively. If, on the other hand, alcohol or acetone solutions of the intermediates **2** and **3** were treated with drops of dilute alkali, royal purple colors were immediately imparted. When stock solutions of compounds **2** and **3** in alcohol (10^{-4} *M*) were diluted with 0.1 *N* alkali, only transient violet colors were observed.

Registry No.—**2**, 13388-72-2; **3**, 13388-73-3; **4**, 13388-74-4; **5**, 13421-38-0.

(13) L. F. Fieser, *J. Am. Chem. Soc.*, **48**, 3201 (1926).

(14) (a) Quinolinequinones: J. Matheus, *Ber.*, **21**, 1887 (1888); R. Long and K. Schofield, *J. Chem. Soc.*, 3161 (1953). (b) Furanonaphthoquinones: S. C. Hooker, *J. Am. Chem. Soc.*, **58**, 1163 (1936).

The Selective Reduction of a Nitro and Pyridyl Group

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In this Note, we wish to report our findings on the stereochemistry of the 1,3-dioxane obtained from the condensation of 2-pyridinecarboxaldehyde and 2-nitro-2-methyl-1,3-propanediol and some selective hydro-