Regiochemical Control in Diels–Alder Routes to Aza-anthraquinone Derivatives

Kevin T. Potts,* Debkumar Bhattacharjee, and Eileen B. Walsh

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181, U.S.A.

Quinoline- and isoquinoline-5,8-diones react with 1-methoxycyclohexa-1,3-diene at 80 °C, the former giving 8-methoxy-1-aza-anthraquinone regiospecifically and the latter 5-methoxy-2-aza-anthraquinone regioselectively; in similar cycloadditions, substituted naphtho- and azanaphtho-quinones react with 1-dimethylamino-3-methyl-1-azabuta-1,3-diene at room temperature forming substituted mono- and di-aza-anthraquinones in high yields with high selectivity.

Cycloadditions between substituted naphtho- and azanaphtho-quinones and appropriate dienes offer an attractive route to functionalized aza-anthraquinones providing that control of the regiochemistry of the cycloaddition can be maintained as in the naphthoquinone series.[1] This communication describes efficient and regioselective syntheses of substituted aza- and diaza-anthraquinones providing practical access to an important group of anthraquinone derivatives of intense current interest in cancer chemotherapy.[2]

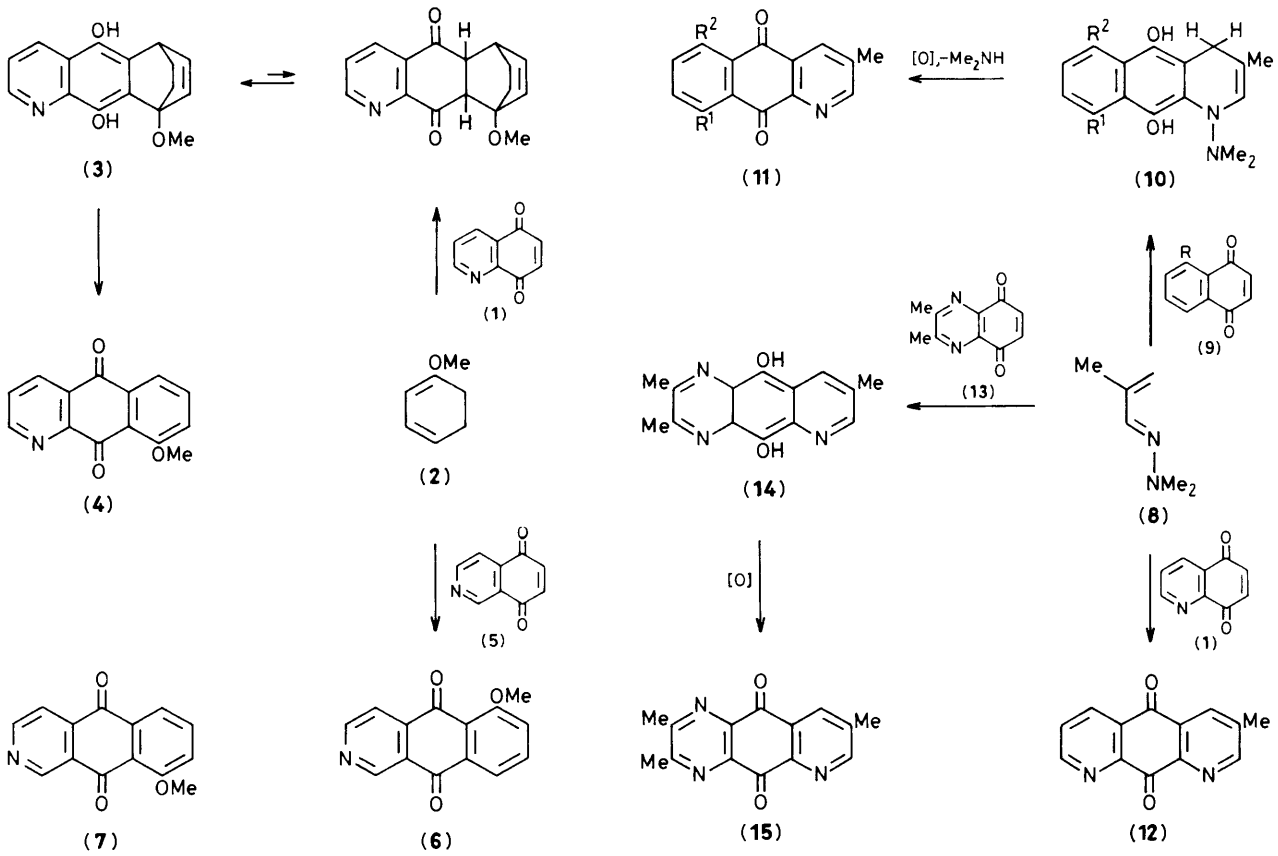
Quinoline-5,8-dione (**1**) and 1-methoxycyclohexa-1,3-diene (**2**) underwent cycloaddition in refluxing benzene (24 h) to give, after oxidation with Ag_2O in 1,2-dimethoxyethane (DME) and thermal elimination of ethylene from the isolable tautomeric intermediate (**3**), a crude mixture of regioisomers in which the 8-methoxy isomer (**4**) was present (>90%).† Purification by crystallization from ethyl acetate gave yellow needles (54%), m.p. 198—199 °C, of the 8-methoxy isomer‡ (**4**) as the only isolable product, and the cycloaddition may be considered to be regiospecific.[3]

The diene (**2**) and isoquinoline-5,8-dione (**5**) also underwent ready cycloaddition in refluxing benzene (24 h) to give a mixture of products comprising the 1 : 1 cycloadducts and their tautomers (ν_{OH} 3300—2800 cm^{-1}). This mixture, on oxidation at room temperature in DME with Ag_2O in the dark, and heating the resultant quinone mixture at 150—160 °C (5 min), resulted in the observable loss of ethylene and the formation of a 2.8:1 mixture† of the regioisomers (**6**) and (**7**). Recrystallization from ethyl acetate afforded 5-methoxy-2-aza-anthraquinone[4] (**6**) as the major product (40%), which formed yellow needles, m.p. 203—205 °C.

The above structural assignments were verified by unambiguous syntheses of both the 5- and 8-methoxy isomers of both

† Determined by n.m.r. integration of the expanded aromatic region of the 4-proton for (**4**) and the 1-proton for (**6**) and (**7**). Refinement of the chemical shifts and coupling constants, and spectral simulation for (**6**) were carried out using a Lame Program on a Varian XL-200 n.m.r. spectrometer.

‡ Satisfactory analytical data (±0.4%, C, H, N) and spectral characteristics (i.r., n.m.r., and mass) were consistent with the assigned structures.



series using heteroatom-directed lithiation[4] routes utilizing, *e.g.* *N,N*-diethyl-*o*- and *m*-anisamide[5] and pyridine-2-carbaldehyde for the 1-aza-anthraquinone derivatives.

These results establish that in the cycloaddition of an electron-rich diene with an azanaphthoquinone the position of the carbonyl group relative to the ring nitrogen atom provides control of the regiochemistry in the cycloaddition, a 2-carbonyl group resulting in essentially a regiospecific cycloaddition, whereas with a 4-carbonyl group the cycloaddition is regioselective. These observations are consistent with the relative electron deficiencies of the respective carbonyl groups[6] and allow structural assignments to be made with azanaphthoquinones and more complex electron-rich dienes such as Danishefsky's diene.

In a complementary approach[7] to aza-anthraquinones, cycloaddition of 1-dimethylamino-3-methyl-1-azabuta-1,3-diene[8] (**8**) (methacrolein *N,N*-dimethylhydrazone) with 5-hydroxynaphthoquinone (**9**; R = OH) occurred in anhydrous benzene at room temperature overnight. Removal of the benzene and heating the residue in ethanol on a steam-bath for 2 h completed the oxidation of the intermediate (**10**), and 8-hydroxy-3-methyl-1-aza-9,10-anthraquinone (**11**; R^1 = OH, R^2 = H) crystallized from the ethanol on cooling. It crystallized from ethyl acetate as orange needles‡ (83%), m.p. 225—226 °C. Assignment of this structure is in accord with the known directing effect of the 5-hydroxy group in analogous Diels–Alder reactions with Danishefsky's diene where the cycloaddition was highly regioselective.[9]

With 5-methoxynaphthoquinone (**9**; R = OMe) under the same conditions, 5-methoxy-3-methyl-1-aza-9,10-anthraquinone‡ (**11**; R^1 = H; R^2 = OMe) was obtained (62%) as yellow microneedles, m.p. 198—200 °C from methanol. This cycloaddition was highly regioselective since the donor effect of the methoxy group diminishes the electron-withdrawing ability of the 4-carbonyl group so that reaction with the nucleophilic end of the diene occurs at C-3. This is in contrast to the 5-hydroxy group which acts as an internal Lewis acid so that C-2 of the naphthoquinone becomes β to the more electron-deficient carbonyl group.[10]

Under analogous conditions the diene (**8**) and quinoline-5,8-dione (**1**) gave 3-methyl-1,8-diaza-9,10-anthraquinone‡ (**12**) as greenish-yellow needles (73%) from ethanol, m.p. 290—300 °C (decomp.). High regioselectivity in this cycloaddition is consistent with the regiochemical control exerted by the position of the ring nitrogen atom relative to the carbonyl group observed in the conversion of (**1**) into (**4**) above. In the reaction of quinoxaline-5,8-dione (**13**), the benzene was removed from the reaction mixture to afford a deep red product identified‡ as the dihydroxy compound (**14**) (79%). This separated from acetonitrile as red needles, m.p. 210—212 °C (decomp.), and when heated in ethanol the dihydroxy compound (**14**) underwent slow oxidation to the quinone (**15**). This triaza-anthraquinone‡ crystallized from ethanol as greenish yellow needles (75%), m.p. 238—240 °C (decomp.).

These results illustrate a convenient route to a variety of substituted aza-anthraquinones from readily available starting materials. The regiochemistry of the Diels–Alder reaction can be effectively controlled by both substituent effects and heteroatom postion in the naphthoquinones, the azadiene being an electron-rich dienic component of predictable regioselectivity.

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3 Quinoline-5,8-dione has been reported (A. J. Birch, D. N. Butler, and J. B. Siddal, *J. Chem. Soc.*, 1964, 2941) to react with 1-methoxycyclohexa-1,3-diene to give a 2:3 mixture of the 5-methoxy- and 8-methoxy-1-aza-anthraquinones, separable by chromatography and whose structures were assigned on the basis of ν_{CO}.

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