THE REGIOSELECTIVE BROMINATION OF 4,4-DIMETHYL-5,8-DIHYDROXY-4*H*-NAPHTHALEN-1-ONE

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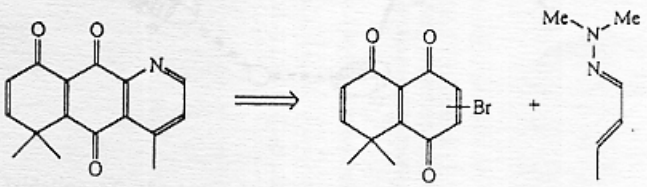
ABSTRACT: Methods for the regioselective bromination of the title naphthalenone are described, which lead to isomeric hydroquinones 5 or 6..

As part of our interest in the synthesis and properties of potentially bioactive azaanthracenedi- and triones, we envisaged the preparation of compound **1** using a Diels-Alder reaction of the bromoquinone **2** and the azadiene **3**.[1]



1 **2** **3**

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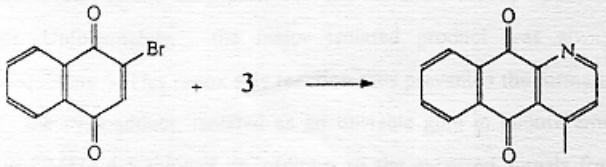
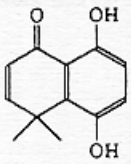
This approach was prompted by the successful cycloaddition of the same azadiene and 2-bromo-1,4-naphthoquinone, reported by Bracher as a synthetic route to the rare azaanthraquinone alkaloid cleistopholine [2]



In order to obtain the bromoquinone **2**, we needed to develop regioselective methods for the bromination/oxidation of the previously described 4,4-dimethyl-5,8-dihydroxy-4*H*-naphthalen-1-one **4** [3]



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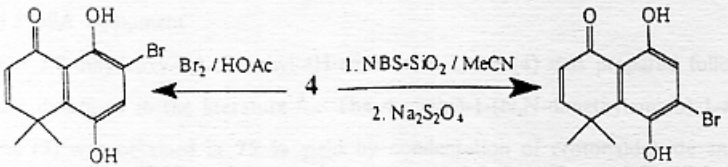
We tackled this problem in two ways. Firstly, by a two-step method, involving bromination of **4** by standard reaction with Br_2/HOAc, followed by an oxidation of the resulting bromohydroquinone. Alternatively, the one-pot bromination/oxidation method employed in the preparation of 2-bromo-1,4-naphthoquinone [4], suggested to us a more direct route to **2** using N-bromosuccinimide (NBS) as the brominating and oxidizing agent.

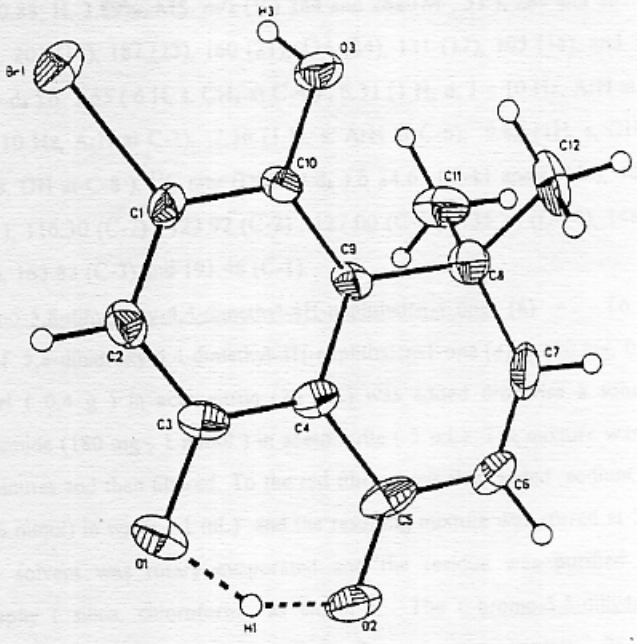
The reaction of the hydroquinone **4** with bromine in acetic acid led to the formation of the regioisomer **5** in 39 % yield. The alternative use of NBS-silica in acetonitrile led to a



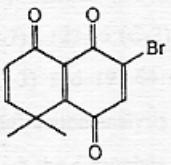
5 **6**

quinone, generated by the oxidation of the other brominated regioisomer 6. Compound 6 could be isolated in 20 % yield, by the *in situ* reduction of the NBS bromination-oxidation product with sodium dithionite.

The characterization of isomers **5** and **6** was based on their ^{1}H and ^{13}C nmr spectra. Further confirmation of the site of bromination was obtained by X-ray diffraction analysis of a monocrystal of **6**, shown below in an Ortep projection.



Oxidation of the bromohydroquinone **5** to the corresponding quinone **7** was achieved by the use of NBS-silica in acetonitrile.



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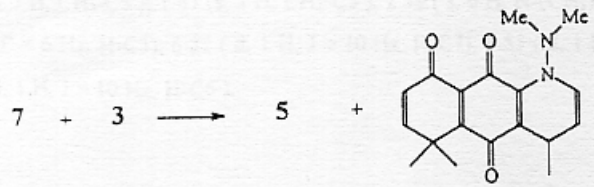
This compound, characterized by its ^{1}H nmr spectrum, proved rather unstable and was utilized without further purification in our subsequent attempts of cycloaddition with the dienophile 3. This reaction was carried out in dichloromethane, and required an excess of the dienophile for the isolation of any appreciable amount of a cycloadduct. Unfortunately, the major isolated product was always the reduced bromohydroquinone 5. This redox side reaction thus prevented the formation of a reasonable amount of the cycloadduct, isolated as an unstable gum in minute amount. Its ^{1}H nmr spectrum in DMSO-d_6 showed, in addition to the expected signals for the dimethylated trione skeleton, a doublet at δ 1.03 which integrated to three protons, and a singlet at δ 2.59 (6 H), which confirmed the presence of an NMe_2 group. Additional signals at δ 5.16 (dd, 1 H, J = 8 Hz, J' = 6 Hz) and at δ 6.55 (d, 1 H, J = 8 Hz) could be ascribed to two =CH protons of a dihydropyridine ring, suggesting structure 9 for the adduct. Because of the low yield of the reaction, no further work was carried out with this compound.



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Experimental:

Melting points were taken with a Koffler hot-stage apparatus and were not corrected. Nmr spectra were recorded with a Bruker AMX 300 MHz equipment, employing tetramethylsilane as internal standard. Ir spectra were obtained with a Perkin Elmer 750 spectrophotometer. The mass spectrum of compound 5 was obtained with a Hewlett-Packard 5989A equipment.

The 5,8-dihydroxy-4,4-dimethyl-4H-naphthalen-1-one (4) was prepared following a procedure described in the literature [3]. The 4-methyl-1-(N,N-dimethylamino)-1-aza-1,3-butadiene (3) was obtained in 75 % yield by condensation of crotonaldehyde and N,N-dimethylhydrazine hydrochloride [5] following a reported procedure [1].

7-Bromo-5,8-dihydroxy-4,4-dimethyl-4H-naphthalen-1-one (5) - To a cooled (5-8 °C) solution of 5,8-dihydroxy-4,4-dimethyl-4H-naphthalen-1-one (4) (0.2 g, 1 mmol) in acetic acid (36 mL) was added dropwise a 1 M solution of Br_2 in acetic acid (1.1 mL). The stirred solution was allowed to react for 48 h at 20°C. It was then poured into ice water (80 mL), and the separated product was filtered and recrystallized in methanol-dichloromethane to give 0.11 g (39% yield) of 7-bromo-5,8-dihydroxy-4,4-dimethyl-4H-naphthalen-1-one , as orange crystals which decomposed at 245°C. Analysis C, 50.75; H, 3.98%. $C_{12}H_{11}O_3Br$ requires C, 50.88; H, 3.89%. MS m/z (%) 284 and 282 (M^+, 57), 269 and 267 (100), 241 and 239 (18), 203 (14), 187 (23), 160 (21), 135 (24), 131 (17), 103 (16), and 77 (27). ^1H nmr (DMSO-d_6) δ 1.55 (6 H, s, CH_3 at C-4) ; 6.31 (1 H, d, J = 10 Hz, ArH at C-2), 7.19 (1H, d, J = 10 Hz, ArH at C-3); 7.36 (1 H, s, ArH at C-6); 9.82 (1H, s, OH at C-5) , 13.25 (1 H, s, OH at C-8). ^{13}C nmr (DMSO-d_6) δ 24.63 (C-11 and C-12), 40.00 (C-4) , 107.96 (C-8), 116.30 (C-7) , 123.92 (C-2) , 127.00 (C-6), 135.34 (C-10), 148.57 (C-9) , 152.17 (C-5), 163.83 (C-3) and 191.46 (C-1).

6-Bromo-5,8-dihydroxy-4,4-dimethyl-4H-naphthalen-1-one (6) - To a stirred suspension of 5,8-dihidroxy-4,4-dimethyl-4H-naphthalen-1-one (4) (100 mg, 0.49 mmol) and silica gel (0.4 g) in acetonitrile (20 mL) was added dropwise a solution of N-bromosuccinimide (180 mg , 1 mmol) in acetonitrile (5 mL). The mixture was stirred for further 15 minutes and then filtered. To the red filtrate was then added sodium dithionite (104 mg, 0.6 mmol) in water (1 mL) and the resulting mixture was stirred at 20°C for 15 minutes.The solvent was rotary evaporated and the residue was purified by column chromatography (silica, chloroform as eluent). The 6-bromo-5,8-dihydroxy-4,4-dimethyl-4H-naphthalen-1-one was isolated in the form of orange crystals, 28 mg (20 % yield), m.p. 150-151°C . Analysis C, 50.60; H, 3.74 %. $C_{12}H_{11}O_3Br$ requires C, 50.88; H, 3.89%. ^1H rmn (DMSO-d_6) δ 1.63 (6 H, s, CH_3 at C-4); 6.35 (1 H, d, J=10 Hz, ArH at C-2); 7.21 (1H, d, J = 10 Hz, ArH at C-3); 7.22 (1 H, s, ArH at C-7); 8.96 (1H, s, OH at C-5) ; 12.82 (1 H, s, OH at C-8). ^{13}C nmr (DMSO-d_6) δ 25.12 (C-11 and C-12), 40.32 (C-4) , 115.30 (C-8), 119.51 (C-7) , 123.95 (C-2) , 124.00 (C-6), 139.82 (C-10), 144.66 (C-9) , 156.47 (C-5), 163.35 (C-3) and 191.64 (C-1). Unambiguous assignment of the structure was obtained by X-ray diffraction analysis of a monocrystal.

Reaction of quinone 7 with the dienophile 3 - To a stirred suspension of the bromo compound 5 (139 mg, 0.49 mmol) in acetonitrile (20 mL) and silica gel (1 g) was added

dropwise a solution of NBS (140 mg , 0.8 mmol) in acetonitrile (35 mL). After 15 minutes, the reaction mixture was filtered and the solvent rotary evaporated to yield 126 mg (92 %) of the crude 7-Bromo-4,4-dimethyl-4H-naphthalene-1,5,8-trione (7) in the form of a red solid which slowly decomposed on standing. The trione was identified by its ^{1}H nmr spectrum in DMSO-d_6 , δ 1.46 (6 H, s, CH_3 at C-4) ; 6.26 (1 H, d, J = 10 Hz, ArH at C-2); 7.01 (1 H, d, J = 10 Hz, ArH at C-3); 7.54 (1 H, s, ArH at C-6). The crude quinone 7 was redissolved in 20 mL of acetonitrile and to the resulting solution was added 55 mg (0.5 mmol) of the dienophile **3**. After 15 minutes at 25°C the mixture was rotary evaporated and the residue column-chromatographed (Sephadex-LH20, methanol as eluent) to yield compound 5 as the major product. A second fraction was separated and purified by chromatography (silica gel, $CHCl_3$ as eluent), yielding a dark violet gum, which weighed 3 mg and that was identified as the 1-(N,N-dimethylamino)-4,5,5-trimethyl-1,4,5,8-tetrahydro-1-azaanthracene-8,9,10-trione (**9**) , ^{1}H nmr (DMSO-d_6) δ 1.03 (d, 3 H, J = 6.6 Hz, CH_3-C4); 1.45 (s, 3 H, CH_3-C5); 1.47 (s, 3 H, CH_3-C5); 2.59 (s, 6 H, N-$(CH_3)_2$); 5.16 (dd, 1 H, J = 8 Hz, J' = 6 Hz, H-C3); 6.22 (d, 1 H, J = 10 Hz, H-C7), 6.55 (d, 1 H, J = 8 Hz, H-C2); 6.98 (d, 1 H, J = 10 Hz, H-C6).

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