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SYNTHESIS OF AZAANTHRAQUINONE DERIVATIVES VIA A HETERO DIELS-ALDER REACTION

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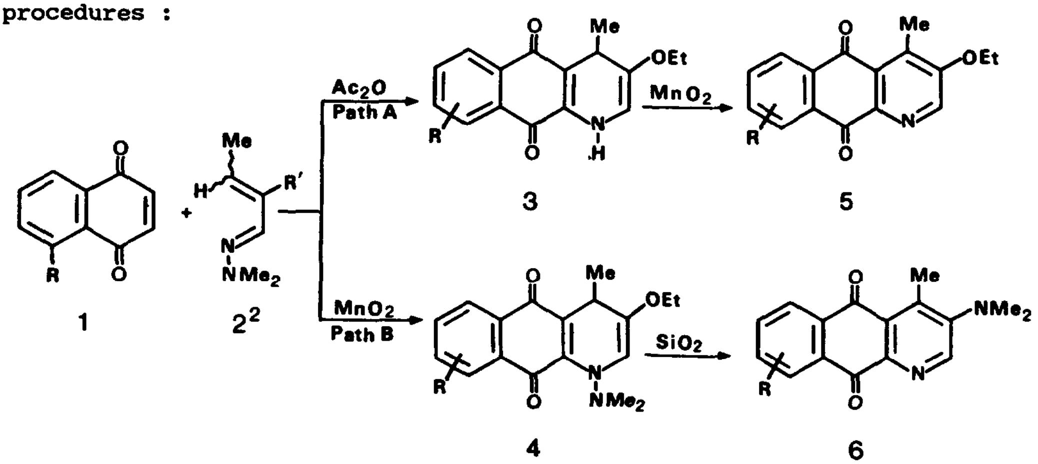
Summary : Azaanthraquinone derivatives with various substituents in the benzene and pyridine rings are prepared by cycloadditions of 1-(dimethylamino)-3-ethoxy-4-methyl-1-azabuta-1,3-diene with 5-substituted naphthoquinones.

As part of research on new azaanthraquinones with potential antitumoral or antifungal activities, the Diels-Alder reaction between naphthoquinones 1 and azadiene 2 (R'=H) has been investigated.[1] Aromatization of the adducts has afforded a facile and regioselective procedure for the synthesis of 4-methyl-5- or 8-hydroxy (or methoxy) azaanthraquinones. In order to introduce functionalization in the pyridine ring, we have now examined the ability of azadiene 2 (R'= OEt) to provide through modulated techniques, azaanthraquinone derivatives with various substituents in the benzene and the pyridine rings. For this purpose, the cycloadditions with 5-substituted naphthoquinones 1 were performed according to the following procedures :



3a, 5a : R = 8-OH ; 5c : R = 8-OMe ; 3e, 4e, 5e, 6e : R = 8-OAc
4d, 6d : R = 5-OMe ; 3f, 4f, 5f, 6f : R = 5-OAc

In path A, the cycloadditions were carried out in the presence of acetic anhydride in order to avoid a nucleophilic attack of the liberated amine[1] upon the naphthoquinones 1 or the 1,4-dihydro azaanthraquinones 3. In the cycloaddition with naphthoquinone 1 (R = OAc), addition of silicagel was necessary to accelerate the formation of the regioisomeric acetates 3e and 3f.

In path B, addition of activated manganese dioxide to the reaction mixture led to the N-dimethylamino derivatives 4d, 4e and 4f. These structures are stable enough to be isolated and identified.

The regiochemistry of the cycloadditions is indicated in Table I.

TABLE I[(a)]

Naphtho-quinones 1	Path	Azadiene 2 (R'=OEt)	Time[(b)]	Adducts	Yield %[(c)]	Ratio of regioisomers[(d)] 1,8- : 1,5-
R = OH	A	1.5 eq	15 min	3a	90	100 : 0
R = OAc	A	1.5 eq	45 min	3e + 3f	45	45 : 55
R = OMe	B	2.5 eq	4 h	4d	40	0 : 100
R = OAc	B	2.5 eq	4 h	4e + 4f[(e)]	23	45 : 55

(a) All the reactions were run in freshly distilled chloroform at 0°C, under a nitrogen atmosphere and in the dark. For typical procedures see notes.[3,4]
(b) The evolution of the reaction was followed by TLC.
(c) Yields were calculated from the isolated pure products.
(d) The isomeric purity and the ratio of regioisomers were evaluated from their 300 MHz ^{1}H-NMR spectra. Representative data are given in note.[5]
(e) The acetyl derivatives are isolated as a mixture of regioisomers.

We have found that azadiene 2 (R' = OEt) is very reactive towards 5-hydroxy naphthoquinone. Moreover, it reacts faster than 2 (R' = H) and under milder conditions (Table I). It is also apparent from Table I that its cycloadditions with 1 (R = OH, OMe) are regiospecific. The structure of 3a is in agreement with the known directing effect of the 5-hydroxy group in juglone in analogous Diels-Alder reactions.[6] The opposite regiochemistry in 4d is also in good agreement with that given by similar azadienes.[1,7] On the contrary, 5-acetoxy naphthoquinone gave a poor regioselectivity. Assignment of the structure of 3e and 3f was made after their oxidation[8] into 5e and 5f and comparison of their ^{1}H-NMR spectral data with those of a sample of 5e.[9]

Aromatization[10] of the N-dimethylamino derivatives 4 into 6 was accompanied with a nucleophilic displacement of the ethoxy group by dimethylamine.[11]

The yields and melting points of compounds 5 and 6 are given in Table II. Representative ^{1}H-NMR data are given in note.[12]

TABLE II

Compound	m.p. [°C]	Yield %
5a	274 (dec)	68
5c[12]	232 (dec)	82
5e[9]	260 (dec)	74
6d	187 (dec)	70
6e*	174 (dec)	65
6f*		

* Isolated as a mixture of regioisomers.

Thus, the cycloadditions described above can provide through modulated oxidative techniques an attractive route to azaanthraquinone derivatives with various substituents in the benzene and pyridine rings.
Satisfactory analytical and spectral data have been obtained for all new compounds reported in this work.

References and notes.

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3 - In a typical procedure in path A, acetic anhydride (0.28 g, 1 eq.) in $CHCl_3$ and silicagel (Amicon, size 35-70 MY, 6 g) were added in one portion to a cooled and stirred chloroformic solution of 5-acetoxy naphthoquinone (0.6 g, 2.78 mmol). Then, azadiene 2 (R' = OEt, 0.65 g, 1.5 eq.) in $CHCl_3$ was slowly added. Stirring and cooling were continued for 45 min. The dark blue coloured solution was separated by filtration and the silicagel washed with CH_2Cl_2. The organic layer was then evaporated under vacuo and recrystallized from AcOEt/hexane (2:8). Compounds 3e and 3f are isolated as a mixture (m.p. 191°C).

4 - In a typical procedure in path B, activated manganese dioxide (1.3g, 10 eq.) was added to a cooled and stirred chloroformic solution of 5-methoxy naphthoquinone. Then, azadiene 2 (R' = OEt, 0.615 g, 2.5 eq.) in $CHCl_3$ was added over 2 h. Stirring and cooling were continued for 2 h. After the usual work-up, compound 4d was purified by column chromatography on alumina using AcOEt/hexane (2:8) as the eluent.

5 - 3a : m.p. 200°C ; ^{1}H-NMR (300MHz, $CDCl_3$) δ ppm : 11.51 (1H, s,OH), 7.63 (1H, dd, J = 7.5 and 1.5 Hz, H-7), 7.58 (1H, dd, J = 7.8 and 7.5 Hz, H-6), 7.10 (1H, dd, J = 7.8 and 1.5 Hz, H-5), 6.72 (1H, br s, NH), 5.64 (1H, d, J = 4.8 Hz, H-2), 3.93 (1H, q, J = 6.5 Hz, H-4), 3.76 (2H, dq, J = 6.5 and 2.4 Hz, CH_2), 1.35 (3H, t, J = 7 Hz, CH_3, 1.27 (3H, d, J = 6.5 Hz, CH_3-4).
4d : m.p. 151°C ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm : 7.59 (1H, dd, J = 7.6 and 1 Hz, H-6), 7.48 (1H, dd, J = 8.2 and 7.8 Hz, H-7), 7.16 (1H, d, J = 8.2 Hz, H-8), 5.56 (1H, s, H-2), 3.91 (3H, s, CH_3O), 3.77 to 3.70 (3H, m, H-4 and CH_2), 2.62 (6H, s, $(CH_3)_2N$), 1.29 (3H, t, CH_3) 1.16 (3H, d, CH_3-4).

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7 - K.T.Potts, D.Bhattacharjee, E.B.Walsh, J. Chem. Soc. Chem. Commun., 1984, 114 and K.T.Potts, E.B.Walsh, D.Bhattacharjee, J. Org. Chem., 1987, **52**, 2285.

8 - Oxidation of a mixture of 3e and 3f into 5e and 5f (m.p. 230°C with dec. ; 88 % yield) was performed with activated MnO_2 as described in reference[1]. Compound 5a was prepared in the same manner from 3a.

9 - 5e was prepared by acetylation of 5a as described for 5-acetoxy naphthoquinone by A. Benthsen, A.Semper, Ber. Dtsch. Chem. Ges., 1914, **47**, 2796.

10 - This aromatization was carried out over silicagel as follows : Compound **4d** (0.1 g, 0.24 mmol) in $CHCl_3$ was stirred at room temperature with silicagel (1 g) for 30 min. After the usual work-up, compound **6d** was chromatographied on silicagel using AcOEt as the eluent.

11 - A displacement of a t-butyldimethylsilyloxy substituent by a dimethylamino group has been reported to occur in a similar aromatization by L.Ghosez, B.Serckx-Poncin, M.Rivera, P.Bayard, F.Sainte, A.Demoulin, A.-M.Frisque-Hesbain, A.Mockel, L.Munoz,C.Bernard-Henriet, Lect. Heterocyclic Chem., 1985, **8**, 69.

12 - 5c was prepared by methylation of 5a as described for 5-methoxy naphthoquinone by J.F.Garden, R.H.Thompson, J. Chem. Soc., 1957, 2483.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm : 8.58 (1H, s, H-2), 7.85 (1H, d, J = 7.7 Hz, H-7), 7.71 (1H, dd, J = 8.5 and 7.7 Hz, H-6), 7.32 (1H, d, J = 8.5 Hz, H-5), 4.29 (2H, q, J = 6.9 Hz, CH_2), 4.04 (3H, s, CH_3-O), 2.72 (3H, s, CH_3-4), 1.53 (3H, t, J = 6.9 Hz, CH_3).
6d : ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm : 8.59 (1H, s, H-2), 7.97 (1H, dd, J = 7.7 and 0.7 Hz, H-7), 7.69 (1H, dd, J = 8.3 and 7.8 Hz, H-6), 7.33 (1H, d, J = 8.3 Hz, H-5), 4.04 (3H, s, CH_3-O), 2.94 (6H, s, CH_3-N), 2.70 (3H, s, CH_3-4).

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