REGIOCHEMICAL STUDY IN THE DIELS-ALDER REACTION OF 2-AZAANTHRAQUINON-3-ONES

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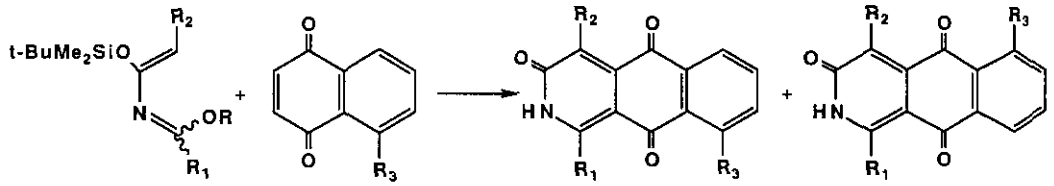
Abstract- The regiochemistry of the Diels-Alder reaction between 2-aza-1,3-butadienes (1) and naphthoquinones (2) (R = OH or OAc) is investigated.

Several examples of [4+2] cycloadditions of 2-aza-1,3-butadienes have been described.[1-5] More recently, 1-alkoxy-3-(t-butyldimethylsilyl)oxy-2-aza-1,3-butadienes (1), readily available from N-acylimidates[6] were reported to react with activated nitriles.[7] In order to get some polysubstituted 2-azaanthraquinon-3-ones, we have carried out their synthesis through a Diels-Alder reaction of 2-azadienes (1) and naphthoquinones (2) (R_3 = OH, OAc) and investigated their regiochemistry :



	R	R_1	R_2		R_1	R_2	R_3		R_1	R_2	R3
1a[7]	i-Pr	H	H	**3a, 4a**	H	H	OH	**5a, 6a**	H	H	OAC
1b[7]	Et	Me	H	**3b, 4b**	Me	H	OH	**5b, 6b**	Me	H	OAc
1c[7]	i-Pr	H	Me	**3c, 4c**	H	Me	OH	**5c, 6c**	H	Me	OAc
1d	Et	Me	Me	**3d, 4d**	Me	Me	OH	**5d, 6d**	Me	Me	OAc

So, azadienes (1) reacted with 5-hydroxy- or 5-acetoxynaphthoquinone to yield cycloadducts which, after aromatization and desilylation,[8] gave a mixture of the substituted 2-azaanthraquinon-3-ones (3) and (4) or (5) and (6) (Table 1).

Table 1. Synthesis of 2-Azaanthraquinon-3-ones

Azadiene (1.5 eq.)	Naphtho-quinone (2)	Time[a] (h)	Products	Yield [%]	Ratio of regio-isomers 2,8:2,5[b]
1a	R_3 = OH	2.5	**3a** + **4a**	77	84:16
1b	R_3 = OH	4	**3b** + **4b**	64	91:9
1c	R_3 = OH	4	**3c** + **4c**	43	82:18
1d	R_3 = OH	2.5	**3d** + **4d**	38	78:22
1a	R_3 = OAc	4.5	**5a** + **6a**	36	37:63
1b	R_3 = OAc	8	**5b** + **6b**	32	30:70
1c	R_3 = OAC	5	**5c** + **6c**	29	43:57
1d	R_3 = OAc	6.5	**5d** + **6d**	20	54:46

(a) The reactions were followed by tlc.
(b) The ratio of regioisomers was evaluated from the ^{1}H-nmr spectra of the crude mixture (see Table 2). The same ratio was generally observed in the isolated pure material excepted in the case of **5c** + **6c** where the yellow precipitate was constituted by the pure regioisomer (**6c**).

It is apparent from Table 1 that the cycloadditions are more regioselective with juglone (**2**) (R = OH) than with acetyljuglone. Moreover, azadiene (**1b**) gives a best regioselectivity with the two naphthoquinones. The structures of compounds (3) are in good agreement with the known directing effect of the 5-hydroxy group in juglone in analogous Diels-Alder reactions.[9] The poor regioselectivity and the generally opposite regiochemistry observed with acetyljuglone[10] are also in accord with the literature.[11]

Identification of the regioisomeric 2-azaanthraquinon-3-ones was established from their ^{1}H-nmr 300 MHz spectra (Table 2). Thus, in the 8-hydroxylated derivatives (3), the peri-OH signals are more deshielded than those of the 5-hydroxylated **4**. Furthermore, in compounds (3), the R_1 substituent (H or Me) is shifted to the lower fields while in **4**, R_2 (H or Me) is deshielded.

Assignement of the structure of the acetates (5) and (6) was made after their hydrolysis (5 % aqueous NaOH)[12] and comparison of the ^{1}H-nmr spectral data of the hydrolysed products with those of compounds (3) and (**4**) prepared directly from juglone. We have also observed that the R_1

substituent (H or Me) was more deshielded after deacetylation of 5 than R_2 (H or Me), while the reverse was obtained with the regioisomeric acetates (6).

Table 2. ^{1}H-Nmr Spectral Data of 2-Azaanthraquinon-3-ones (300 MHz, DMSO-d_6, δ ppm)

	NH	OH		R_1(H or Me)		R_2(H or Me)		$OCOCH_3$	
		8-OH	5-OH	2,8- regioisomers	2,5- regioisomers	2,8- regioisomers	2,5- regioisomers	2,8- regioisomers	2,5- regioisomers
3a + 4a	12.84	12.84	12.25	8.47	8.37	6.90	6.97		
5a + 6a	12.85			8.39	8.33	6.82	6.87	2.39	2.37
3b + 4b	12.82	13.11	12.10	2.76	2.74	6.81	6.91		
5b + 6b	12.70			2.67	2.75	6.79	6.74	2.36	2.39
3c + 4c	12.78	12.77	12.45	8.32	8.24	2.46	2.53		
5c + 6c	12.67			8.16	8.22	2.47	2.49	2.36	2.38
3d + 4d	12.74	13.08	12.35	2.74	2.70	2.42	2.45		
5d + 6d	12.59			2.61	2.70	2.39	2.36	2.35	2.29

EXPERIMENTAL PART

Melting points were taken in capillary tube using a Büchi 510 apparatus and are corrected. Ir spectra were performed on a Perkin-Elmer 1310 spectrophotometer. ^{1}H-Nmr spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-24B or at 300 MHz on a Bruker AM 300 spectrometer. Mass spectra were performed by direct ionisation (EI at 70 eV) on an AE1 MS 902 apparatus. Elemental analysis were made at the Centre de Microanalyse du CNRS at Solaise. Azadienes (**1a**, **1b**, and **1c**) were prepared according to Ph. Bayard procedure.[7] These azadienes are stable at -25°C during two or three weeks, but they decompose quickly at room temperature.

SYNTHESIS OF ETHYL (N-PROPIONYL)ACETIMIDATE

Triethylamine (15 ml) was added to a stirred solution of ethyl acetimidate hydrochloride (6 g, 0.049 mol) in dry dichloromethane (65 ml) at -30°C. Then 4.3 ml (0.049 mmol) of freshly distilled propionyl chloride were

quickly added. Petroleum ether (120 ml) was added to the reaction mixture and the cooling bath was removed. The solid was filtered off and the filtrate was concentrated in vacuo. The residue was again dissolved in petroleum ether (60 ml) and any insoluble material was removed by filtration. The solution was concentrated and the residue was distilled through a 10 cm Vigreux column. Yield: 5.7 g (83%). bp_{27mmHg} 78-79°C. Ir (film): 1690, 1660 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 60 MHz): δ 3.90 (2H, q, J = 6.5 Hz); 2.15 (2H, q, J = 7.0 Hz); 1.80 (3H, s); 1.12 (3H, t, J = 6.5 Hz); 0.92 (3H, t, J = 7.0 Hz). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.52; H, 8.78; N, 9.47.

SYNTHESIS OF 3-AZA-4-(t-BUTYLDIMETHYLSILYL)OXY-2-ETHOXY-2,4-HEXADIENE (**1d**)

A mixture of ethyl (propionyl)acetimidate (3 g, 21 mmol) and anhydrous triethylamine (3.2 ml) in dry ether (15 ml) was treated with t-butyldimethylsilyl triflate (5.76 g, 21.8 mmol) diluted in ether (6ml). Two phases were obtained. The upper ethereal phase was removed and the lower phase was washed twice with dry ether (2.10 ml). The combined ethereal fractions were concentrated in vacuo and distilled through a 10 cm Vigreux column. Yield: 3.8 g (70%). $bp_{0.5mmHg}$ 76-77°C. Ir (film): 1690, 1660 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 60 MHz): δ 3.90 (2H, q, J = 6.5 Hz); 3.60 (1H, q, J = 6.5 Hz); 1.80 (3H, s); 1.40 (3H, d, J = 6.5 Hz); 1.10 (3H, t, J = 6.5 Hz); 0.78 (9H, s); -0.02 (6H,s).

SYNTHESIS OF 2-AZAANTHRAQUINON-3-ONES. GENERAL PROCEDURE

A solution of 2-aza-1,3-diene (**1**) (2.52 mmol) and naphthoquinone (**2**) (1.68 mmol) in chloroform (5 ml) was stirred and heated under nitrogen at 70°C for a variable time (see Table 1). Then, an aqueous solution of 40% hydrofluoric acid (0.27 ml) was added at room temperature and the mixture was stirred for 2 h. After evaporation of the solvent, the residue was heated in acetone (10 ml) under reflux for 2 h. The precipitate was constituted by a mixture of the regioisomers (**3**) and (**4**) or (**5**) and (**6**). It was isolated by filtration and recritallized from acetone.

2-Aza-8- and 2-aza-5-hydroxy-9,10-anthraquinon-3-ones, (**3a**) and (**4a**)

mp > 300°C (acetone). Ir (KBr): 3220-3120, 1725, 1680, 1640 cm^{-1}. ^{1}H-Nmr (DMSO-d_6,300 MHz): **3a**: δ 12.84 (2H, s, OH and NH); 8.47 (1H, s, H-1); 7.83 (1H, H-6, dd, J = 7.5 and 8.0 Hz); 7.75 (1H, H-5, d, J = 8.0 Hz); 7.39 (1H, H-7, d, J = 7.5 Hz); 6.97 (1H, s, H-4). **4a**: δ 12.84 (1H, s, NH);

12.25 (1H, s, OH); 8.37 (1H, s, H-1); 7.83 (1H, H-7, dd, J = 7.5 and 8.0 Hz); 7.75 (1H, H-8, d, J = 8.0 Hz); 7.38 (1H, H-6, d, J = 7.5 Hz); 6.90 (1H, s, H-4). Anal. Calcd for $C_{13}H_7NO_4$, 0.66 H_2O: C, 61.66; H, 3.05; N, 5.53. Found: C, 61.61; H, 2.84; N 5.59. Hrms Calcd for $C_{13}H_7NO_4$: M^+ 241.0375. Found: 241.0361.

2-Aza-8- and 2-aza-5-hydroxy-1-methyl-9,10-anthraquinon-3-ones, (**3b**) and (**4b**)
mp > 300°C (acetone). Ir (KBr): 3600-3400, 1670, 1635 cm^{-1}. ^{1}H-Nmr (DMSO-d_6, 300 MHz): **3b:** δ 13.11 (1H, s, OH); 12.82 (1H, s, NH); 7.73 (1H, H-6, dd, J= 7.0 and 8.2 Hz); 7.62 (1H, H-5, d, J = 7.0 Hz); 7.33 (1H, H-7, d, J= 8.2 Hz); 6.81 (1H, s, H-4); 2.76 (3H, s, CH_3-1). **4b:** δ 12.10 (H, s, OH); 12.10 (1H, s, NH); 7.73 (1H, H-7, dd, J = 7.0 and 8.8 Hz); 7.62 (1H, H-8, d, J = 7.0 Hz) ; 7.33 (1H, H-6, d, J = 8.8 Hz); 6.88 (1H, s, H-4); 2.76 (3H, s, CH_3-1). Anal. Calcd for $C_{14}H_9NO_5$, 0.5 H_2O: C, 63.64; H, 3.43; N, 5.30. Found: C, 63.59; H, 3.43; N, 5.14. Hrms Calcd for $C_{14}H_9NO_5$: M^+ 255.0532. Found: 255.0527.

2-Aza-8- and 2-aza-5-hydroxy-4-methyl-9,10-anthraquinon-3-ones, (**3c**) and (**4c**)
mp > 300°C (acetone). Ir (KBr): 3600-3270, 1700, 1640 cm^{-1}. ^{1}H-Nmr (DMSO-d_6, 300 MHz): **3c:** δ 12.78 (1H, s, NH); 12.77 (1H, s, OH); 8.31 (1H, s, H-1); 7.77 (1H, H-6, dd, J = 7.7 and 8.2 Hz); 7.65 (1H, H-5, d, J = 7.4 Hz); 7.33 (1H, H-7, d, J = 8.2 Hz); 2.46 (3H, s, CH_3-4). **4c:** δ 12.78 (1H, s, NH); 12.45 (1H, s, OH); 8.24 (1H, s, H-1); 7.77 (1H, H-7, dd, J = 7.7 and 8.2 Hz); 7.62 (1H, H-8, d, J = 8.2 Hz); 7.23 (1H, H-6, d, J = 8.1 Hz); 2.53 (3H, s, CH_3-4). Anal. Calcd for $C_{14}H_9NO_4$, 0.5 H_2O: C, 63.68; H, 3.81; N, 5.30. Found: C, 63.46; H, 3.55; N, 5.28. Hrms Calcd for $C_{14}H_9NO_4$: M^+ 255.0531. Found: 255.0538.

2-Aza-8- and 2-aza-5-hydroxy-1,4-dimethyl-9,10-anthraquinon-3-ones, (**3d**) and (**4d**)
mp > 300°C (acetone). Ir (KBr): 3600-3300, 1690, 1632 cm^{-1}. ^{1}H-Nmr (DMSO-d_6, 300 MHz): **3d:** δ 13.08 (1H, s, OH); 12.74 (1H, s, NH); 7.72 (1H, H-6, dd, J = 7.8 and 7.8 Hz); 7.59 (1H, H-5, d, J = 7.8 Hz); 7.31 (1H, H-7, d, J = 7.8 Hz); 2.74 (3H, s, CH_3-1), 2.42 (3H, s, CH_3-4). **4d:** δ 12.74 (1H, s, NH); 12.35 (1H, s, OH); 7.72 (1H, H-7, dd, J = 7.8 and 7.8 Hz); 7.59 (1H, H-8, d, J = 7.8 Hz); 7.31 (1H, H-6, d, J = 7.8 Hz); 2.74 (3H, s, CH_3-1);

2.42 (3H, s, CH_3-4). Anal. Calcd for $C_{15}H_{11}NO_4$, 1.1 H_2O: C, 62.32; H, 4.60; N, 4.84. Found: C, 62.23; H, 4.24; N, 4.77. Hrms Calcd for $C_{15}H_{11}NO_4$: M^+ 269.0688. Found: 269.0679.

8-Acetoxy- and 5-acetoxy-2-aza-9,10-anthraquinon-3-ones, (**5a**) and (**6a**)
mp 250-253°C decomp. (acetone). Ir (KBr): 1765, 1690, 1640 cm^{-1}. ^{1}H-Nmr (DMSO-d_6, 300 MHz): **5a**: δ 12.85 (1H, s, NH); 8.39 (1H, s, H-1); 8.18 (1H, H-5, d, J= 7.3 Hz); 7.98 (1H, H-6, dd, J = 7.3 and 7.4 Hz); 7.62 (1H, H-7, d, J = 7.4 Hz); 6.82 (1H, s, H-4); 2.39 (3H, s, $COCH_3$). **6a**: δ 12.85 (1, s, NH); 8.32 (1H, s, H-1); 8.16 (1H, H-8, d, J = 7.2 Hz); 7.93 (1H, H-7, dd, J = 7.2 and 7.4 Hz); 7.64 (1H, H-6, d, J = 7.4 Hz); 6.87 (1H, s, H-4); 2.37 (3H, s, $COCH_3$). Anal. Calcd for $C_{15}H_9NO_5$: C, 63.61; H, 3.20; N, 4.95. Found: C, 63.75; H, 3.39; N, 4.67. Hrms Calcd for $C_{15}H_9NO_5$: M^+ 283.0481. Found: 283.0476.

8-Acetoxy- and 5-acetoxy-2-aza-1-methyl-9,10-anthraquinon-3-ones, (**5b**) and (**6b**)
mp > 270-280°C decomp. (acetone). Ir (KBr): 1772, 1675, 1660 cm^{-1}. ^{1}H-Nmr (DMSO-d_6, 300 MHz): **5b**: δ 12.70 (1H, s, NH); 8.13 (1H, H-5, d, J = 7.4 Hz); 7.90 (1H, H-6, dd, J = 7.4 and 8.0 Hz); 7.60 (1H, H-7, d, J = 8.0 Hz); 6.79 (1H, s, H-4); 2.67 (3H, s, CH_3-1); 2.36 (3H, s, $COCH_3$). **6b**: δ 12.70 (1H, s, NH); 8.08 (1H, H-8, d, J = 7.4 Hz); 7.95 (1H, H-7, dd, J = 7.4 and 8.0 Hz); 7.57 (1H, H-6, d, J = 8.0 Hz); 6.74 (1H, s, H-4); 2.75 (3H, s, CH_3-1); 2.38 (3H, s, $COCH_3$). Anal. Calcd for $C_{16}H_{11}NO_5$, 0.16 H_2O: C, 64.00; H, 3.69; N, 4.64. Found: C, 63.98; H, 3.55; N, 4.59. Hrms Calcd for $C_{16}H_{11}NO_5$: M^+ 297.0637. Found: 297.0628.

8-Acetoxy- and 5-acetoxy-2-aza-4-methyl-9,10-anthraquinon-3-ones, (**5c**) and (**6c**)
mp 265-271°C decomp. (acetone). Ir (KBr): 1767, 1675, 1646 cm^{-1}. ^{1}H-Nmr (DMSO-d_6, 300 MHz): **5c**: δ 12.67 (1H, s, NH); 8.16 (1H, s, H-1); 8.11 (1H, H-5, d, J = 7.1 Hz); 7.90 (1H, H-7, dd, J = 7.1 and 8.0 Hz); 7.59 (1H, H-6, d, J = 8.0 Hz); 2.47 (3H, s, CH_3-4); 2.36 (3H, s, $COCH_3$). **6c**: δ 12.67 (1H, s, NH); 8.22 (1H, s, H-1); 8.09 (1H, H-8, d, J = 7.1 Hz); 7.93 (1, H-6, dd, J = 7.1 and 8.1 Hz); 7.59 (1H, H-7, d, J = 8.1 Hz); 2.49 (3H, s, CH_3-4); 2.38 (3H, s, $COCH_3$). Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.69; H, 3.73; N, 4.71. Found: C, 64.60; H, 3.84; N, 4.67. Hrms Calcd for $C_{16}H_{11}NO_5$: M^+ 297.0637. Found: 297.0639.

8-Acetoxy- and 5-acetoxy-2-aza-1,4-dimethyl-9,10-anthraquinon-3-ones, (**5d**) and (**6d**)

mp 250-253°C decomp. (acetone). Ir(KBr): 1768, 1650, 1641 cm^{-1}. ^1H-Nmr (DMSO-d_6, 300 MHz): **5d:** δ 12.59 (1H, s, NH); 8.00 (1H, H-5, dd, J = 1.1 and 7.8 Hz); 7.84 (1H, H-6, dd, J = 7.8 and 8.0 Hz); 7.56 (1H, H-7, dd, J = 1.1 and 8.0 Hz); 2.61 (3H, s, CH_3-1); 2.39 (3H, s, CH_3-4); 2.35 (3H, s, $COCH_3$). **6d:** δ 12.59 (1H, s, NH); 8.01 (1, H-8, dd, J = 1.1 and 7.8 Hz); 7.84 (1H, H-7, dd, J = 7.8 and 8.0 Hz); 7.53 (1H, H-6, dd, J = 1.1 and 8.0 Hz); 2.70 (3H, s, CH_3-1); 2.36 (3H, s, CH_3-4); 2.29 (3H, s, $COCH_3$). Anal. Calcd for $C_{17}H_{13}NO_5$, 0.25 H_2O: C, 64.66; H, 4.23; N, 4.43 Found: C, 64.66; H, 4.35; N, 4.69. Hrms Calcd for $C_{17}H_{13}NO_5$: M^+ 311.0794. Found: 311.0795.

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12. A mixture of the regioisomeric acetates (**5d**) and (**6d**) (0.06 g, 0.19 mmol) was stirred at room temperature for 2 h with 5 ml of an aqueous solution of 5 % sodium hydroxide. Then, the hydroxylated derivatives (**3d**) and (**4d**) were precipitated by addition of an aqueous solution of 5 % hydrochloric acid.

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