Studies on the Oxidative Addition of *N,N*-Dimethylamine to Bromojuglones and Bromomethyljuglones

Leila CHAKER, Félix PAUTET, and Houda FILLION*

Laboratoire de Chimie Organique, Institut des Sciences Pharmaceutiques et Biologiques, Université Claude Bernard Lyon I, 8 Avenue Rockefeller, 69373 Lyon Cedex 08, France. Received April 27, 1994; accepted June 10, 1994

The nucleophilic addition of dimethylamine to bromojuglones and bromomethyljuglones is followed by elimination of hydrogen bromide or oxidation. With 2-bromojuglone, the oxidative process predominates at low temperature. The regiochemistry of the addition is a function of the temperature and of the position of the bromine atom (C-2 or C-3) on the quinone.

Keywords bromojuglone; bromomethyljuglone; dimethylamine; nucleophilic addition; regioselectivity

In an earlier study,[1] we observed during the Diels–Alder reaction of crotonaldehyde *N,N*-dimethylhydrazone with juglone in acetonitrile, the formation of the two regioisomeric dimethylamino juglones as by-products (ratio of 2-amino/3-amino: 3/2). Similar observations were reported in the cycloadditions of another *N,N*-dimethylamino-1-azadiene with naphthazarine and azanaphthoquinones.[2,3] Formation of these amino derivatives resulted from a nucleophilic addition–oxidation on the starting quinones by dimethylamine liberated from the unstable primary adducts.

Starting with 2- or 3-bromojuglone, the addition of dimethylamine was follwed by two competitive reactions. On one hand, elimination of hydrogen bromide gave the 2- and 3-dimethylamino-5-hydroxynaphthoquinones previously observed and on the other hand, an oxidative process led to the formation of 2- (or 3-) bromo-3- (or 2-) dimethylaminojuglones. In order to identify these latter derivatives and to investigate the possibility that a bromine atom might exert a stronger regiochemical control towards a nucleophile than a 5-substituent on naphthoquinone, we carried out, under the same experimental conditions, the direct addition of dimethylamine to juglone, methyljuglone and their 2- and 3-bromo derivatives.

Results and Discussion

Oxidative Addition of Dimethylamine to Juglone 1a and Methyljuglone 1b The direct addition of amines to 5-substituted naphthoquinones was previously described. The addition at room temperature of an aqueous solution of dimethylamine to a suspension of juglone in water affords the 2-dimethylamino derivative,[4] while the reaction of aniline with methyljuglone gives the 3-anilino compound.[5] The observed regiochemistry for these nucleophilic additions is consistent with the directing effect of the 5-substituent of the corresponding naphthoquinones in their Diels–Alder reactions towards electron-rich dienes.[6] Thus, a 5-hydroxyl group favors nucleophile attack at C-2, while the 5-methoxyl group affords the 3-substituted derivative. We performed all the nucleophilic additions in freshly distilled toluene at various temperatures (−70, −20, 0 and 110 °C). Under the experimental conditions we used, the oxidative addition of dimethylamine to juglone **1a** and methyljuglone **1b** gave a mixture of the 2- and 3-dimethylamino derivatives **2** and **3** (Chart 2, Table I).

At low temperatures (−70 to −20 °C), the oxidative addition was highly regioselective with juglone and regiospecific with methyljuglone. Furthermore, an inversion of the regiochemistry was observed with the latter as compared with that of 5-hydroxynaphthoquinone. Moreover, an increase in temperature was accompanied with a decrease in regioselectivity. So, the usually reported directing effects of the 5-hydroxyl and 5-methoxyl groups were only well maintained below 0 °C.

Addition of Dimethylamine to 2-Bromojuglone 4a and 2-Bromomethyljuglone 4b Starting with 2-bromonaphthoquinones **4a** and **4b**, a mixture of compounds **2**, **3** and **5** was obtained. The 2-bromo-3-dimethylamino derivatives **5** were formed through an addition–oxidation process while the aminoquinones **2** and **3** were generated by addition of dimethylamine and elimination of hydrogen bromide (Chart 3, Table II).

Formation of compounds **3** and **5** corresponds to

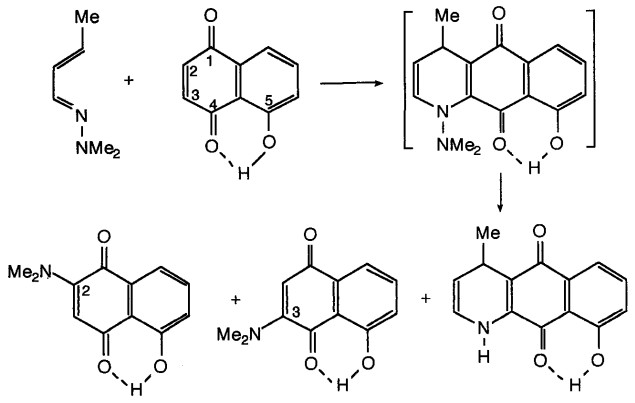
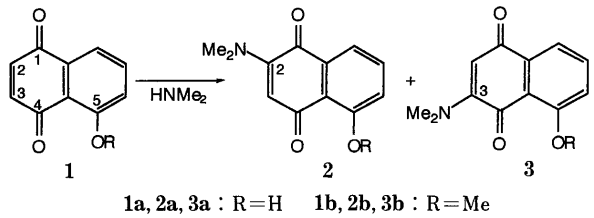


Chart 1



1a, 2a, 3a : R=H **1b, 2b, 3b** : R=Me

Chart 2

TABLE I. Addition of Dimethylamine to Juglone **1a** and Methyljuglone **1b** as a Function of Temperature

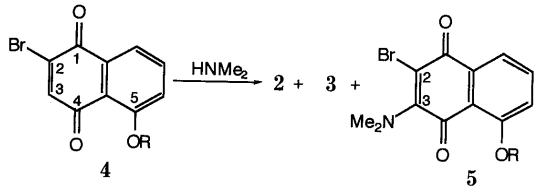
Temp. (°C)	Quinone	Adduct	Yield [%]	Ratio **2a/3a**	Quinone	Adduct	Yield [%]	Ratio **2b/3b**
−70	**1a**	**2a+3a**	88	97/03	**1b**	**2b+3b**	67	0/100
−20	**1a**	**2a+3a**	86	95/05	**1b**	**2b+3b**	70	0/100
0	**1a**	**2a+3a**	75	87/13	**1b**	**2b+3b**	71	06/ 94
110	**1a**	**2a+3a**	60	47/53	**1b**	**2b+3b**	55	29/ 71

Yields and ratios were calculated from isolated pure products.

TABLE II. Addition of Dimethylamine to 2-Bromojuglone **4a** and 2-Bromomethyljuglone **4b** as a Function of Temperature

Temp. (°C)	Quinone	Adducts	Yield [%]	Ratio **2a/3a+5a**	Ratio **3a/5a**	Quinone	Adducts	Yield [%]	Ratio **2b/3b+5b**	Ratio **3b/5b**
−70	**4a**	**2a+3a+5a**	62	0/100	11/89	**4b**	**2b+3b+5b**	95	0/100	80/20
−20	**4a**	**2a+3a+5a**	65	16/ 84	29/71	**4b**	**2b+3b+5b**	96	0/100	85/15
0	**4a**	**2a+3a+5a**	62	24/ 76	68/32	**4b**	**2b+3b+5b**	90	0/100	98/02
110	**4a**	**2a+3a+5a**	73	63/ 37	91/09	**4b**	**2b+3b+5b**	86	0/100	98/03

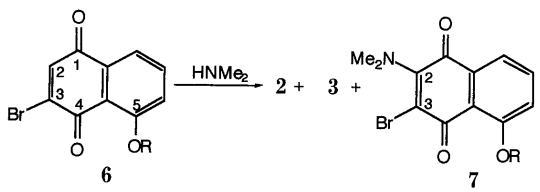
Yields and ratios were calculated from isolated pure products.



4 5

2a, 3a, 4a, 5a : R=H **2b, 3b, 4b, 5b** : R=Me

Chart 3



6 7

2a, 3a, 6a, 7a : R=H **2b, 3b, 6b, 7b** : R=Me

Chart 4

TABLE III. Addition of Dimethylamine to 3-Bromojuglone **6a** and 3-Bromomethyljuglone **6b** as a Function of Temperature

Temp. (°C)	Quinone	Adducts	Yield [%]	Ratio **2a+7a/3a**	Ratio **2a/7a**	Quinone	Adducts	Yield [%]	Ratio **2b+7b/3b**	Ratio **2b/7b**
−70	**6a**	**2a+3a+7a**	97	100/ 0	67/33	**6b**	**2b+3b+7b**	96	89/11	74/26
−20	**6a**	**2a+3a+7a**	90	100/ 0	95/05	**6b**	**2b+3b+7b**	97	84/16	73/27
0	**6a**	**2a+3a+7a**	85	95/05	100/ 0	**6b**	**2b+3b+7b**	95	67/33	95/05
110	**6a**	**2a+3a+7a**	75	93/07	100/ 0	**6b**	**2b+3b+7b**	81	51/48	95/05

Yields and ratios were calculated from isolated pure products.

nucleophilic attack of dimethylamine at C-3 of the corresponding quinones **4**. With 2-bromojuglone **4a**, the regiochemistry of the addition and the ratio of **3a**/**5a** are functions of the temperature. Thus, at −70 °C the reaction occurs only at C-3, the orientating effect of the bromine atom being stronger than that of the 5-hydroxyl group. Moreover, the addition–oxidation product **5a** is the major one. An analogous nucleophilic addition of a transoid diene to 2-bromojuglone **4a** was previously reported to take place at −78 °C without hydrogen bromide elimination.[7] An increase in temperature produces a decrease in regioselectivity, and formation of the addition–elimination product **3a** predominates. With 2-bromomethyljuglone **4b**, the nucleophilic addition was regiospecific at various temperatures. Only the 3-amino derivatives **3b**+**5b** were obtained. This regiochemistry results from the cumulative influences of both the electron-donating 5-methoxyl group on C-3 and the blocking effect of the bromine atom at C-2.

Addition of Dimethylamine to 3-Bromojuglone 6a and 3-Bromomethyljuglone 6b As above, formation of the amino quinones **2** and **3** was accompanied with that of the 3-bromo-2-dimethylamino derivatives **7** (Chart 4, Table III).

The addition of dimethylamine to 3-bromojuglone **6a** is regiospecific at low temperatures and highly regioselective even at 110 °C. Thus, the nucleophilic attack at C-2 is favored by the directing effect of the 5-hydroxyl group and the blocking effect of the bromine atom. Concerning the two competitive processes, elimination of hydrogen bromide or oxidation (**2a**/**7a** ratio), we observed that compound **2a** was either the major product (−70 to −20 °C) or the sole one (0 to 110 °C). Analogous addition–eliminations have been reported by Thomson[4,8] to occur, under reflux in ethanol, in the reactions of dimethylamine and aniline with 3-halogenojuglones. The 3-dimethylamino or 3-anilino juglone was the only regioisomer isolated. This anomalous regiochemistry, which is in conflict with the blocking effect of the halogen on C-3, was pointed out by Thomson. Starting with 3-bromomethyljuglone, and due to the opposite directing

effects on C-2 of the 5-methoxyl group and the bromine atom, the nucleophilic addition was regioselective only at low temperatures. Furthermore, as with the 2-bromonaphthoquinones, oxidative-addition occurred in part to give compounds **7a** and **7b**.

Conclusion

The yields and the regioselectivity of the addition of dimethylamine on 5-substituted naphthoquinones were generally enhanced by the use of low temperatures. When 2- or 3-bromo-5-substituted naphthoquinones were used, the corresponding amino quinones **2** or **3** were obtained through addition of dimethylamine and elimination of hydrogen bromide with some bromo derivatives **5** or **7** resulting from an addition–oxidation reaction. The yields of the latter were greatly decreased by an increase in temperature. Concerning the nucleophilic additions on these 2- or 3-bromonaphthoquinones unsymmetrically substituted on the benzene ring, the observed regioselectivity clearly indicates that the bromine atom exerts a stronger regiochemical control than the 5-substituent.

Experimental

Melting points were taken in a capillary tube with a Buchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 apparatus. ^{1}H-NMR spectra were obtained on a Bruker AM 300 spectrometer using Me_4Si as an internal standard. Coupling constants (J) are given in Hz. TLC was performed on silica gel (Merck) plates with a fluorescent indicator (254 nm). Column chromatography was carried out on silica gel using hexane/ethyl acetate (30/70) as the eluent. Microanalyses were done at the centre de Microanalyse du CNRS at Solaise, France.

All reactions were carried out in anhydrous toluene. 2-Bromojuglone **4a** was prepared by oxidation of 1,5-diacetoxynaphthalene with *N*-bromosuccinimide[7] followed by hydrolysis of the 5-acetate. Compound **4b**[9] was obtained by methylation of **4a** according to the procedure used to prepare methyljuglone **1b**.[10] 3-Bromojuglone **6a** was prepared by treating juglone with bromine in glacial acetic acid.[8] By this procedure we also obtained 2-bromojuglone **4a** (13% yield), which was eliminated by recrystallization from acetone. The methyl derivative **6b**[9] was prepared as described for the quinone **4b**. Melting points of bromonaphthoquinones **4** and **6** were identical with the values reported in the literature.[8,9]

General Procedure for the Addition of Dimethylamine to Substituted Naphthoquinones Dimethylamine (75 μl, 0.6 mmol) was added through a syringe and under nitrogen to a cooled (−70, 20, 0 °C) or refluxed (110 °C) solution of the corresponding naphthoquinone (0.4 mmol) in toluene (5 ml). The reaction mixture was magnetically stirred. The yellow solution quickly turned red. The reaction was followed by TLC to monitor the disappearance of the starting quinone, which was completly consumed in all cases within 30 min. Removal of toluene gave a red product, which was purified by column chromatography.

2-*N*,*N*-Dimethylamino-5-hydroxy-1,4-naphthoquinone (2a) mp 141 °C (lit.,[4] mp 147 °C). IR (KBr) 1665, 1610 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 12.90 (1H, s, 5-OH), 7.42 (1H, dd, J=7.5, 2.0, 8-H), 7.38 (1H, t, J=7.5, 7-H), 7.12 (1H, dd, J=7.5, 2.0, 6-H), 5.63 (1H, s, 3-H), 3.18 (6H, s, 2-NMe_2), 5.63 (1H, s, 3-H).

2-*N*,*N*-Dimethylamino-5-methoxy-1,4-naphthoquinone (2b) mp 97 °C. IR (KBr) 1670, 1620 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.64 (1H, dd, J=7.6, 1.1, 8-H), 7.55 (1H, dd, J=8.2, 7.6, 7-H), 7.26 (1H, dd, J=8.2, 1.1, 6-H), 5.81 (1H, s, 3-H), 3.98 (3H, s, 5-OMe), 3.15 (6H, s, 2-NMe_2). *Anal.* Calcd for $C_{13}H_{13}NO_3 \cdot 0.3\ H_2O$: C, 65.83; H, 5.80; N, 5.90. Found: C, 65.58; H, 5.75; N, 5.75.

3-*N*,*N*-Dimethylamino-5-hydroxy-1,4-naphthoquinone (3a) mp 152 °C (lit.,[4] mp 156 °C). IR (KBr) 1615 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.87 (1H, s, 5-OH), 7.57 (2H, dd, part AA′ of an AA′X system, 7-H, 8-H), 7.14 (1H, t, part X of an AA′X system, 6-H), 5.83 (1H, s, 2-H), 3.23 (6H, s, 3-NMe_2).

3-*N*,*N*-Dimethylamino-5-methoxy-1,4-naphthoquinone (3b) mp 118 °C. IR (KBr) 1665, 1620 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.71 (1H, dd J=7.7, 1.1, 8-H), 7.62 (1H, dd, J=8.2, 7.7, 7-H), 7.18 (1H, dd, J=8.02, 1.0, 6-H), 5.91 (1H, s, 2-H), 3.98 (3H, s, 5-OMe), 3.22 (6H, s, 3-NMe_2). *Anal.* Calcd for $C_{13}H_{13}NO_3 \cdot 0.2\ H_2O$: C, 66.51; H, 5.75; N, 5.96. Found: C, 66.57; H, 5.65; N, 5.90.

2-Bromo-3-*N*,*N*-dimethylamino-5-hydroxy-1,4-naphthoquinone (5a) mp 134 °C. IR (KBr) 1630 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.83 (1H, s, 5-OH), 7.67 (1H, dd, J=8.4, 0.9, 8-H), 7.57 (1H, dd, J=8.4, 7.4, 7-H), 7.18 (1H, dd, J=8.4, 0.9, 6-H), 3.25 (6H, s, 3-NMe_2). *Anal.* Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.77; H, 3.46; N, 4.71.

2-Bromo-3-*N*,*N*-dimethylamino-5-methoxy-1,4-naphthoquinone (5b) mp 112 °C. IR (KBr) 1680, 1630 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.83 (1H, s, 5-OH), 7.80 (1H, dd, J=7.6, 0.9, 8-H), 7.68 (1H, dd, J=8.4, 7.6, 7-H), 7.20 (1H, d, J=8.4, 6-H), 3.98 (3H, s, 5-OMe), 3.26 (6H, s, 3-NMe_2). *Anal.* Calcd for $C_{13}H_{12}BrNO_3$: C, 50.19; H. 3.88; N, 4.50. Found: C, 50.07; H, 3.75; N, 4.59.

3-Bromo-2-*N*,*N*-dimethylamino-5-hydroxy-1,4-naphthoquinone (7a) mp 77 °C. IR (KBr) 1670, 1620 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 12.48 (1H, s, 5-OH), 7.50 (2H, m, 7-H, 8-H), 7.22 (1H, dd, J=7.4, 2.1, 6-H), 3.29 (6H, s, 2-NMe_2). *Anal.* Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.93; H, 3.56; N, 4.69.

3-Bromo-2-*N*,*N*-dimethylamino-5-methoxy-1,4-naphothoquinone (7b) mp 116 °C. IR (KBr) 1665, 1650 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65 (1H, dd, J=8.0, 1.0, 8-H), 7.58 (1H, t, J=8.0, 7-H), 7.26 (1H, d, J=8.0, 6-H), 3.98 (3H, s, 5-OMe), 3.18 (6H, s, 2-NMe_2). HRMS Calcd for $C_{13}H_{12}BrNO_3$: 309.0000. Found: 308.9999.

References

1) M. Chigr, H. Fillion, A. Rougny, *Tetrahedron Lett.*, **29**, 5913 (1988).
2) K. T. Potts, E. B. Walsh, D. Bhattacharjee, *J. Org. Chem.*, **52**, 2285 (1987).
3) C. Gesto, E. de la Cuesta, C. Avendano, *Tetrahedron*, **45**, 4477 (1989).
4) R. H. Thomson, *J. Org. Chem.*, **16**, 1082 (1951).
5) J. W. MacLeod, R. H. Thomson, *J. Org. Chem.*, **25**, 36 (1960).
6) T. R. Kelly, J. W. Gillard, R. N. Goerner, J. M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977).
7) J. R. Grunwell, A. Karipides, C. T. Wigal, S. W. Heinzman, J. Parlow, J. A. Surso, L. Clayton, F. J. Fleitz, M. Daffner, J. E. Stevens, *J. Org. Chem.*, **56**, 91 (1991).
8) R. H. Thomson, *J. Org. Chem.*, **13**, 377 (1948).
9) R. L. Hannan, R. A. Barber, H. Rapoport, *J. Org. Chem.*, **44**, 2153 (1979).
10) J. F. Garden, R. H. Thomson, *J. Chem. Soc.*, **1957**, 2483.