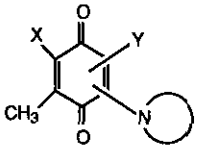
REACTION OF BENZOQUINONES WITH CYCLIC AMINES; ^{1}H- AND ^{13}C-NMR SPECTRA OF AMINE-ADDUCTS

Mitsuo Akiba,* Keiko Nagaoka, Masazumi Takigawa, and Toyozo Takada
Tokyo College of Pharmacy 1432-1 Horinouchi, Hachioji-shi,
Tokyo, Japan

Abstract —— Reaction of unsymmetrical 1,4-benzoquinone with cyclic amines afforded a mixture of amine-adducts. Using dibromoquinone as the substrate, monoamine adduct was obtained regioselectively. Regiochemistry was determined by ^{1}H- and ^{13}C-nmr spectroscopic analyses.

The ability of nitrogen containing compounds to undergo Michael addition with a variety of quinones has been observed and documented in detail.[1] However, with unsymmetrical benzoquinones, it has so far not been possible to obtain regioselective amine-adducts with amines. Recently, Rapoport et al.[2]reported that 2-methoxy-3-methyl-1,4-benzoquinone (**7**) and 2,3-dibromo-5-methoxy-6-methyl-1,4-benzoquinone (**12**) underwent highly regioselective amination with pyrrolidine yielding aminoquinones (**5a** and **13a**) related structurally to mitomycin antibiotics. They determined the regiochemistry of these amine-adducts on the basis of correlation to adducts derived from specifically deuterated quinone intermediates (**8** and **10**) as shown in Scheme 1. However, the structural determination of amine-adducts by the synthetic methodology required many reaction steps.

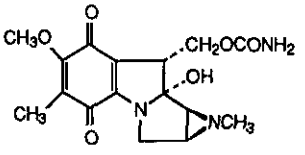
In the synthetic studies on mitomycin antibiotics, we examined the reaction of unsymmetrical 1,4-benzoquinones with cyclic amines and clarified regiochemistry of the amine-adducts obtained from nmr spectroscopic analysis.



2,3,5,6,13

X=Y=H

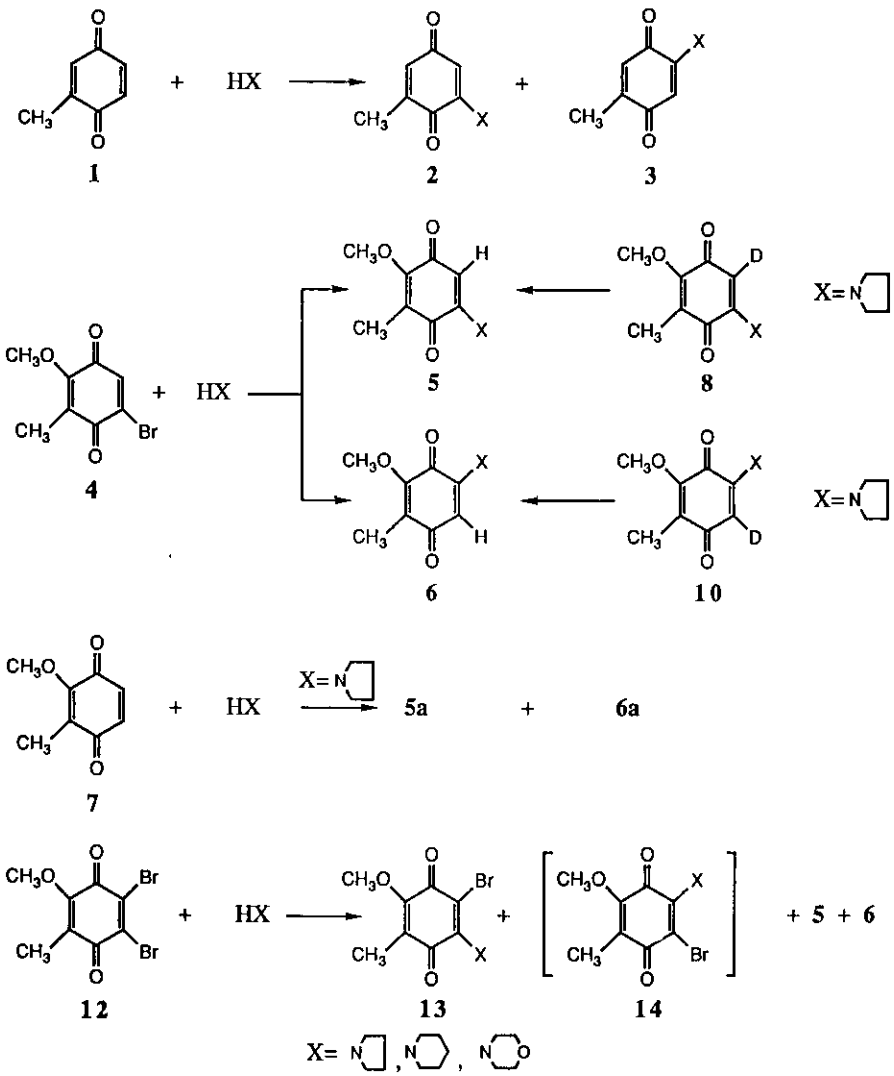
X=CH3O , Y=H or Br



Mitomycin B

Reactions of quinones **1**, **4**, and **12** as unsymmetrical substrates with amines (pyrrolidine, piperidine, and morpholine) were carried out. Amines in slight excess when reacted with **1** at room temperature gave amine-adducts **2** and **3** in moderate yields in a 1/3~2/3 ratio. ^{1}H-Nmr spectroscopic analysis indicated that **3** was the major adduct since a singlet signal corresponding to the olefinic proton of the vinylogous amide at 5.45-5.82 ppm was detected. In the case of **2**, a doublet signal [3] (J=2Hz) corresponding to its proton was observed.

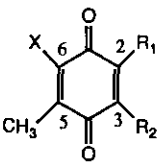
Examination of reactions of monobromoquinone **4**[4] with amines indicated that **4** underwent addition-elimination with amines to give a mixture of amine-adducts **5** and **6** in a 1~3/2 ratio.



Scheme 1

The structures of pyrrolidinoquinone **5a** and **6a** were confirmed by comparision with authentic samples[2] prepared from quinone **7** and pyrrolidine. The ir spectra of compounds **5a**, **5b**, and **5c** or **6a**, **6b**, and **6c** were quite similar to each other, thus making the assignment of their structures easy. Treatment of dibromoquinone **12**[2] with amines under similar conditions gave **13** as the main product, along with small amounts of **5** and **6**. Although Rapoport et al. obtained a mixture of **13** and **14** in a ratio of 98/2 by the same reaction, loss of bromine from **13** and **14** due to light exposure obtained here may possible lead to the production of the corresponding aminoquinones **5** and **6** as reported previously.[2] Thus, using dibromoquinone as the substrate, the monoamine adduct was obtained regioselectively. These amine-adducts are summarized in Tables 1 and 2.

Table 1. Aminoqunones prepared



amine-adduct	X	R_1	R_2	mp (°C)	Yield (%)	mass(m/z) [M^+]	^{1}H nmr ($CDCl_3$)δ [ppm] C_2-H	C_3-H	C_5-CH_3	C_6-H	C_6-OCH_3
2a	H	H	N⌐	110-112	16	191	5.45(d)		2.00(d)[a]	6.46(q)[a]	
3a	H	N⌐	H	116-118	32	191		5.45(s)	2.05(d)[a]	6.33(q)[a]	
2b	H	H	N◯	53-54	16	205	5.76(d)		2.02(d)[a]	6.48(q)[a]	
3b	H	N◯	H	85-86	35	205		5.82(s)	2.04(d)[a]	6.46(q)[a]	
2c	H	H	N◯O	145-146	7	207	5.78(d)		2.03(d)[a]	6.56(q)[a]	
3c	H	N◯O	H	134-135	25	207		5.80(s)	2.04(d)[a]	6.54(q)[a]	
5a	CH_3O	H	N⌐	64-66	45	221	5.30(s)		1.88(s)		4.08(s)
6a	CH_3O	N⌐	H	62-64	44	221		5.40(s)	1.96(s)		3.84(s)
5b	CH_3O	H	N◯	oil	49	235	5.60(s)		1.92(s)		4.08(s)
6b	CH_3O	N◯	H	oil	41	235		5.70(s)	1.96(s)		3.92(s)
5c	CH_3O	H	N◯O	136-138	56	237	5.56(s)		1.90(s)		4.03(s)
6c	CH_3O	N◯O	H	146-148	39	237		5.69(s)	1.94(s)		3.89(s)
13a	CH_3O	Br	N⌐	73	71	300			1.86(s)		4.08(s)
13b	CH_3O	Br	N◯	oil	75	314			1.89(s)		4.03(s)
13c	CH_3O	Br	N◯O	105-107	83	316			1.81(s)		4.03(s)

[a] J=1.8 Hz

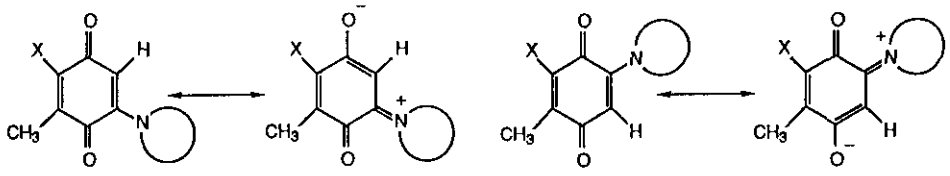
The structure of the isomer in the amine-adduct was confirmed by comparison of the present results with those of Rapoport et al. A structural analysis was also carried out using ^{1}H- and ^{13}C-nmr spectroscopic methods. Nmr data for the amine-adducts are summarized in Tables 1 and 2.

2- and 3-Substituted aminoquinones were found to differ slightly in the chemical shifts of ^{1}H- and ^{13}C-nmr spectra. In ^{1}H-nmr spectrum, generally, the signal of the C-5 methyl of 2-substituted aminoquinone appeared in a slightly low field compared with that of 3-substituted aminoquinone but in contrast, the chemical shift of C_6-H or C_6-OCH_3 in the case of 3-substituted aminoquinone was just the opposite. ^{13}C-Nmr spectroscopic analysis showed essentially the same. All carbon atoms could be clearly distinguished from each other by comparison with those of mitomycins and analogues.[5] The spectrum for the quinone ring carbons can be divided into three regions, low field carbonyl carbons, middle range quinone ring carbons, and saturated carbons at high field. For example, the following carbons were easily assigned for the quinone ring of isomer **2a** and **3a**: **2a**; 185.59 and 185.08 (C-1 or C-4), 147.49 (C-3), 142.21 (C-5), 135.25 (C-6), 101.18 (C-2), 15.43 (C_5-CH_3), **3a**; 185.14 and 184.67 (C-1 or C-4), 148.24 (C-2), 147.31 (C-5), 130.02 (C-6), 101.94 (C-3), 16.09 (C_5-CH_3).

Table 2. ^{13}C-Nmr Data for Aminoquinones

Amine-	Carbon Atom ($CDCl_3$) δ[ppm]							
adduct	C-2	C-3	C-5	C_5-CH_3	C-6	C-1 or C-4		C_6-OCH_3
2a	101.18(d)	147.49(s)	142.21(s)	15.43(q)	135.25(d)	185.59(s)	185.08(s)	-
3a	148.24(s)	101.94(d)	147.31(s)	16.09(q)	130.02(d)	185.14(s)	184.67(s)	-
2b	108.22(d)	152.79(s)	143.57(s)	15.63(q)	133.88(d)	186.18(s)	185.48(s)	-
3b	152.22(s)	107.76(d)	146.51(s)	15.91(q)	133.88(d)	186.18(s)	185.48(s)	-
2c	109.61(d)	152.15(s)	144.03(s)	15.51(q)	133.59(d)	186.29(s)	185.02(s)	-
3c	151.69(s)	109.09(d)	146.45(s)	15.86(q)	132.09(d)	186.71(s)	184.74(s)	-
5a	99.98(d)	147.61(s)	123.39(s)	8.59(q)	157.35(s)	185.59(s)	180.29(s)	61.16(q)
6a	152.83(s)	101.19(d)	131.46(s)	9.23(q)	146.23(s)	185.43(s)	-	60.38(q)
5b	107.59(d)	151.52(s)	125.63(s)	8.82(q)	154.75(s)	186.80(s)	180.59(s)	60.89(q)
6b	152.75(s)	105.40(d)	129.39(s)	8.88(q)	156.02(s)	185.59(s)	181.67(s)	60.37(q)
5c	107.13(d)	152.22(s)	126.10(s)	8.82(q)	153.74(s)	185.25(s)	182.08(s)	61.00(q)
6c	150.77(s)	109.55(d)	129.44(s)	8.88(q)	155.84(s)	186.87(s)	180.18(s)	60.48(q)

A comparison of **2a** and **3a** indicated not only an upfield shift of the C-5 methyl carbon but those of the C-5 carbon in **2a** and C-6 carbon in **3a**. Similar results were obtained for the isomers in other amine-adducts (**2b** and **3b**, **2c** and **3c**, 5a and **6a**). Furthermore, the C-6 methoxy carbon of **5a** appeared slightly down field compared to that of **6a**. These differences are considered due to resonance[6] between forms A and B, or C and D, resulting in partial withdrawal of elactrons from the N-atom and their introduction into the quinone ring, and electron-donating effect of C_5-CH_3 group in forms A and C.



A **B** **C** **D**

X=H , OCH_3

In this conjugate interaction, form B in particular exerts a deshielding effect on substituent X causing its signal in nmr spectrum to shift down field. Form D also had a similar effect on the C-5 methyl group. These nmr spectroscopic results permit the structural assignment of isomers in amine-adducts. The present nmr spectroscopic analysis should greatly facilitate determination of regiochemistry of amine-adducts to a far greater extent than other presently available spectroscopic methods.

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on a Hitachi 260-10 and Hitachi M-80 spectrophotometer, respectively. ^{1}H-Nmr spectra were recorded on a Varian EM-390 and/or a Brucker AM-400 spectrometer. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). Chromatographic separations were made using a silica gel (Wako-gel C-200) column. Thin-layer chromatography (tlc) was carried out with pre-coated silica gel plates (Kiesel 60 F-254, Merck).

Reaction of 2-methyl-1,4-benzoquinone with amines (pyrrolidine, piperidine, and morpholine): To a solution of 2-methyl-1,4-benzoquinone **1** (244 mg, 2 mmol) in chloroform (10 ml), a solution of

pyrrolidine (141 mg, 2 mmol) in chloroform (5 ml) was added and the mixture was stirred for 12 h in dark. Chloroform was evaporated under a reduced pressure and the residue was separated by flash column chromatography over silica gel, using n-hexane-ethyl acetate mixture (2:1). 122 mg of 3-methyl-6-(1-pyrrolidinyl)-1,4-benzoquinone **3a** were obtained from initial fraction and 61 mg of 3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone **2a** from second fraction. **3a:** purple crystals; ir [KBr]: 1670, 1651 cm^{-1}. Ms, m/z 191 (M^+). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.24; H, 6.83; N, 7.30. **2a**: purple crystals; ir [KBr]: 1660, 1640 cm^{-1}. Ms, m/z 191 (M^+). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.35; H, 6.91; N, 7.50. The same reaction and treatment were carried out on **1** and piperidine. 144 mg of 3-methyl-6-(1-piperidinyl)-1,4-benzoquinone **3b** were obtained from initial fraction and 66 mg of 3-methyl-5-(1-piperidinyl)-1,4-benzoquinone **2b** from second fraction. **3b**: purple crystals; ir [KBr]: 1660, 1640 cm^{-1}. Ms, m/z 205 (M^+). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C,70.31; H, 7.38; N, 6.76. **2b**: purple crystals; ir [KBr]: 1665, 1645 cm^{-1}. Ms, m/z 205 (M^+). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.30; H, 7.35; N, 6.79. In the case of morpholine, 104 mg of 3-methyl-6-morpholino-1,4-benzoquinone **3c** and 29 mg of 3-methyl-5-morpholino-1,4-benzoquinone **2c** were obtained. **3c**: purple crystals; ir [KBr]: 1660, 1640, 1620 cm^{-1} Ms, m/z 207(M^+). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.46; H, 6.37; N, 6.21. **2c**: purple crystals; ir [KBr]: 1663, 1642 cm^{-1}. Ms, m/z 207 (M^+). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.76; H, 6.27; N, 6.58. These results are summarized in Tables 1 and 2.

Reaction of 3-bromo-5-methyl-6-methoxy-1,4-benzoquinone **4** with amines (pyrrolidine, piperidine, and morpholine): To a solution of 4 (304 mg, 2 mmol) in chloroform (10 ml), a solution of pyrrolidine (142 mg, 2 mmol) in chloroform (5 ml) was added and mixture was stirred for 12 h in dark. Chloroform was evaporated under a reduced pressure and the residue was separated by flash column chromatography over silica gel, using n-hexane-ethyl acetate mixture (2:1). 194 mg of 2-methoxy-3-methyl-6-(1-pyrrolidinyl)-1,4-benzoquinone **6a** were obtained from initial fraction and 199 mg of 2-methoxy-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone **5a** from second fraction. The obtained compounds **5a** and **6a** here were identical with the authentic samples.[2]

6a: purple red crystals; ir [KBr]: 1670, 1656, 1612 cm^{-1}. Ms, m/z 221 (M^+). **5a:** purple red crystals; ir [KBr]: 1665. 1622 cm^{-1}. Ms, m/z 221 (M^+). The same reaction was carried out on **4** and piperidine or morpholine. 2-Methoxy-3-methyl-6-(1-piperidinyl)-1,4-benzoquinone **6b**: purple oil; ir [NaCl]: 1675, 1653, 1618 cm^{-1}. Ms, m/z 235 (M^+). 2-Methoxy-3-methyl-5-(1-piperidinyl)-1,4-benzoquinone **5b**: purple oil ; ir [NaCl]: 1643, 1618 cm^{-1}. Ms, m/z 235 (M^+).

2-Methoxy-3-methyl-6-morpholino-1,4-benzoquinone **6c**: purple red crystals; ir [KBr]: 1660, 1640, 1625 cm^{-1}. Ms, m/z 235 (M^+). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.20; N, 5.83.

2-Methoxy-3-methyl-5-morpholino-1,4-benzoquinone **5c**: purple red crystals; ir [KBr]: 1660, 1650 cm^{-1}. Ms, m/z 235 (M^+). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.88; H, 6.35; N, 5.78. These results are shown in Tables 1 and 2.

Reaction of 2,3-dibromo-5-methyl-6-methoxy-1,4-benzoquinone with amines (pyrrolidine, piperidine, and morpholine): To dibromoquinone **12** (310 mg, 1 mmol) in benzene (10 ml) was added pyrrolidine (142 mg, 2 mmol) in benzene (10 ml) with rapid stirring in dark and then a mixture was stirred for 6 h. A reaction solution was filtered and evaporated to give a purple crystalline solid.

2-Bromo-3-(1-pyrrolidinyl)-5-methyl-6-methoxy-1,4-benzoquinone **13a** (220 mg, 71%), **5a** (15 mg), and **6a** (8 mg) were isolated from the mixed solid by flash column chromatography over silica gel, using n-hexane-ethyl acetate (3:1). **13a:** purple crystals ; ir [KBr]: 1654, 1615 cm^{-1}. Ms, m/z 299 (M^+). Anal. Calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.78; N, 4.67. Found: C, 47.75; H, 4.72; N, 4,59. The same reaction was carried out on **12** with piperidine or morpholine. 2-Bromo-3-(1-piperidinyl)-5-methyl-6-methoxy-1,4-benzoquinone **13b**: purple *oil. ir [NaCl]: 1660 cm*$^{-1}$. Ms, m/z 313 (M^+). 2-Bromo-3-morpholino-5-methyl-6-methoxy-1,4-benzoquinone **13c**: purple crystals; ir [KBr]: 1650 cm^{-1}. Ms, m/z 315 (M^+). Anal. Calcd for $C_{12}H_{14}BrNO_4$: C, 45.59; H, 4.46; N, 4.43. Found: C, 45.82; H, 4.48; N, 4.43.

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