Pergamon

Tetrahedron Letters 41 (2000) 7475–7480

TETRAHEDRON LETTERS

The regioselectivity in the reaction of 6,7-dihaloquinoline-5,8-diones with amine nucleophiles in various solvents

Eun Young Yoon,[a] Han Young Choi,[b] Kye Jung Shin,[a] Kyung Ho Yoo,[a] Dae Yoon Chi*[b] and Dong Jin Kim[a,*]

[a]*Life Sciences Division, Korean Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, South Korea*

[b]*Department of Chemistry, Inha University, 253 Yonghyun-Dong, Nam-Ku, Inchon 402-751, South Korea*

Received 28 April 2000; revised 19 July 2000; accepted 24 July 2000

Abstract

The regioselectivity in the reaction of 6,7-dihaloquinoline-5,8-diones with amine nucleophiles was described. In this reaction the solvent played an important role.

Keywords: 6,7-dihaloquinoline-5,8-diones; regioselectivity; solvent effect; X-ray crystal structures.

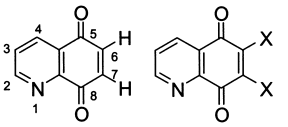
The derivatives of 5,8-quinolinedione have a wide spectra of biological activities such as antitumor, antifungal and antimalarial agents.[1] 5,8-Quinolinediones and 6,7-dihaloquinoline-5,8-diones are useful starting materials for various kinds of these bioactive compounds. Therefore, the regioselectivity and identification in the reaction of these compounds with nucleophiles are important problems. In the case of 5,8-quinolinedione, the 6-position is favored for amine addition because of its electron deficiency. Pratt et al. explained qualitatively this electron deficiency of C6 as an inductive effect.[2] The C8 carbonyl, which is *ortho* to the nitrogen, is more electron deficient than the C5 carbonyl group (*meta* to nitrogen). This electron deficiency of C8 is transferred to C6 and finally leads to preferential C6 substitution by nucleophilic attack. The regioselectivity of the 6-position is greatly increased by coordination with a positive ion to a heterocyclic nitrogen atom and C8 carbonyl in the presence of metal ions such as Ce(III) or Ni(II).[2,3]

On the other hand, the regiochemistry in the reaction of 6,7-dihaloquinoline-5,8-dione with amine nucleophiles has not been found clearly in the literature. Especially, direct methodology

* Corresponding authors. Fax: +82-2-958-5189; e-mail: djk2991@kist.re.kr

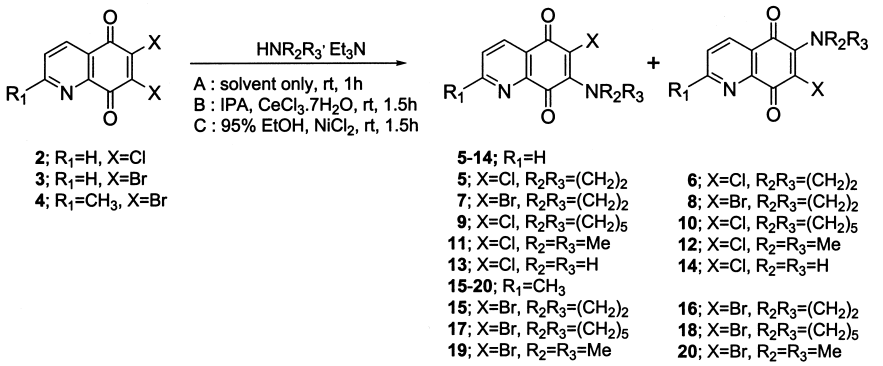
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01278-8

for the synthesis of 7-aminosubstituted quinoline-5,8-diones has been seldom studied in spite of their biological importance. Only Russian chemists reported that a 6-amino compound is a major product in the amination of 6,7-dichloroquinoline-5,8-dione with ammonia in ethanol solvent.[4] During the syntheses of antitumor compounds containing a quinolinedione moiety from 6,7-dihaloquinoline-5,8-diones as a starting material, we found that the solvent played an important role in the reaction of 6,7-dihaloquinoline-5,8-diones with amine nucleophiles.



1 **2**; X=Cl
3; X=Br

Dihaloquinolinedione **2** or **3** reacted readily with aziridine in benzene at room temperature to give two regioisomers which were isolated by column chromatography, although the differences of their R_f values are not distinctive (Scheme 1).[5] To confirm the regiochemistry of products in these reactions, we tried to prepare single crystals of all the products for X-ray crystallography. Fortunately, we were able to obtain a good crystal of minor product in the case of X = Br, and the X-ray crystal diffraction analysis showed 6-aziridinyl-7-bromo-quinolinedione, as depicted in Fig. 1.[6]



Scheme 1.

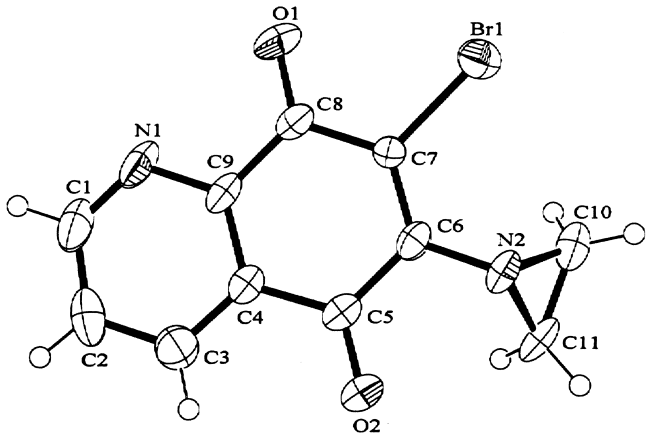


Figure 1. Crystal structure of 6-aziridinyl-7-bromoquinolinedione **8**

These two isomers were characterized from their TLC and ^{1}H NMR spectra. Regardless of the kind of halogen, the R_f values of the 7-aziridinyl isomers were slightly higher than those of the 6-aziridinyl ones in the normal phase system. The R_f values of compounds **5** and **7** were 0.11, where those of compounds **6** and **8** were 0.10, respectively, when developing twice in 1:1 hexane/ethyl acetate as an eluent on the silica gel plate. The ^{1}H NMR spectral data of these isomers showed typical chemical shifts of C2–H and C4–H. The C2–H chemical shifts of the 7-isomers were slightly shifted upfield, while the C4–H ones of the 7-isomers were slightly shifted downfield with respect to those of the 6-isomers (Table 1).

Table 1
Spectral data for quinolinediones

Compound	^{1}H NMR[a]				IR[b]
	C2–H	C3–H	C4–H	Δ(C2–H − C4–H)	$\nu_{C=O}$
5	8.91	7.62	8.37	0.54	1692, 1664
6	8.93	7.62	8.35	0.58	1676
7	8.94	7.63	8.41	0.53	1690, 1650
8	8.97	7.63	8.37	0.60	1672
15	–	7.50	8.34	–	1686, 1648
16	–	7.43	8.18	–	1678

[a] δ Scale from TMS in 300 MHz NMR spectra in $CDCl_3$.
[b] cm^{-1}, KBr pellet.

Although there were only slight differences between the chemical shifts for the corresponding protons of each isomer, the differences between the chemical shift of C2–H and C4–H showed distinctive values. The Δ(C2–H–C4–H) of the 6-isomers (**6** and **8**) were larger than those of the 7-isomers (**5** and **7**). In the case of 2-methylquinoline-5,8-diones (**15**–**20**),[7] the C4–H chemical shifts of the 7-isomers were considerably moved downfield with respect to those of the 6-isomers, as in the case of quinoline-5,8-diones (**5**–**14**). Also, there were distinctive differences between the 6- and 7-isomers in their IR spectra. The carbonyl absorption of the 6-isomers appeared around 1670 cm^{-1} as a single band, while the 7-isomers showed two absorption bands around 1690 and 1650–1660 cm^{-1} due to Fermi resonance.[8] These phenomena are a useful criteria for assigning regiochemistry of aminosubstituted haloquinoline-5,8-diones.

Table 2 represents the regioselectivity in the reaction of 6,7-dichloroquinoline-5,8-dione with aziridine in the presence of triethylamine as a base in various solvents at room temperature. It shows that the solvent plays an important role in this reaction. In aprotic solvent, 7-substitution was much more favorable, while in protic solvent the formation of the 6-isomers increased. In the presence of a cerium ion as a Lewis acid, the reactivity of the 6-position was enhanced, in a similar manner to the case of 5,8-quinolinedione. The effect of the Lewis acid might be maximized in protic alcohol solvents.

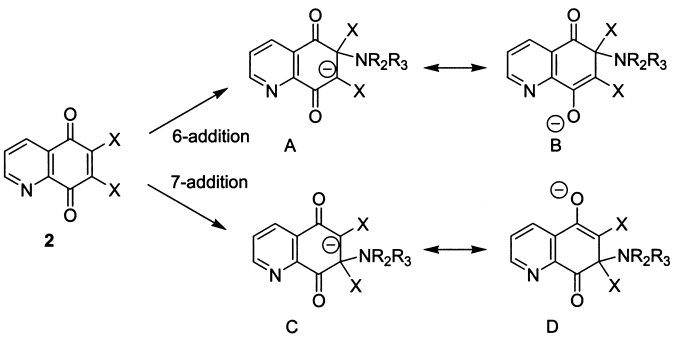
This 6-substitution preference in a polar protic solvent could be considered through a plausible pathway in Scheme 2.[2,3] Intermediate **B**, which is followed by 1,4-addition of amines, could be stabilized through either the formation of complexation between a nitrogen atom and oxide by a Lewis acid or the formation of hydrogen bonds between a nitrogen atom and oxide

Table 2
Regioselectivity in the reaction of 6,7-dichloroquinoline-5,8-dione with aziridine in various solvents

Entry	Solvents	**5**/**6**[a]		Yield (%)[b]	
		Metal salt		Metal salt	
		None	$CeCl_3 \cdot 7H_2O$	None	$CeCl_3 \cdot 7H_2O$
1	Benzene	84/16	80/20	94	93
2	Dioxane	95/5	52/48	89	84
3	THF	96/4	89/11	24	50
4	Dichloromethane	63/37	54/46	94	76
5	DMF	75/25	57/43	62	58
6	Acetonitrile	64/36	61/39	92	85
7	2-Propanol	60/40	5/95	91	85
8	Ethanol	48/52	11/89	92	83
9	Methanol	43/57	19/81	94	87

[a] Analyzed by ^{1}H NMR.
[b] Isolated by column chromatography.

by a protic solvent. On the other hand, intermediate **D** could not be stabilized. But, in this stage we could not explain exactly why 7-substitution was much more favorable in non-polar aprotic solvents.



Scheme 2.

It seems that as the reactivities of piperidine and dimethylamine toward 6,7-dihaloquinoline-5,8-dione are greater than those of aziridine, the regioselectivity with a reactive nucleophile was dropped either in benzene or in dioxane (Table 3, entry 1 versus 2 and 3, and entry 5 versus 6 and 7). The methyl substituent on C2 position decreased the regioselectivity for the formation of 7-amino derivatives (entries 9–11). The position in C2, C3 and C4, as well as the electronic effect of the substituent would greatly affect the regioselectivity between C6 and C7, as shown in the pyridine ring system.[10]

In conclusion, as it has been proven that the 7-amino group in streptonigrin and lavendamycin are important in their antitumor activity, these solvent studies for increasing the regioselectivity of C7 would be useful for the development of 5,8-quinolinedione antitumor agents.

Table 3
Regioselectivity in the reaction of 6,7-dichloroquinoline-5,8-dione or 6,7-dibromo-2-methylquinoline-5,8-dione with various amines

Entry	Reaction condition	HNR_2R_3	Isomers	Ratio[b]	Yield (%)[c]
1	A (benzene)	Aziridine	**5**/**6**	84/16	94
2	A (benzene)	Piperidine	**9**/**10**	61/39	92
3	A (benzene)	Dimethylamine	**11**/**12**	61/39	96
4	A (benzene)	Ammonia	**13**/**14**	85/15	93
5	A (dioxane)	Aziridine	**5**/**6**	95/5	89
6	A (dioxane)	Piperidine	**9**/**10**	82/18	94
7	A (dioxane)	Dimethylamine	**11**/**12**	79/21	99
8	A (dioxane)	Ammonia	**13**/**14**	82/18	89
9	A (dioxane)[a]	Aziridine	**15**/**16**	78/22	90
10	A (dioxane)[a]	Piperidine	**17**/**18**	53/47	89
11	A (dioxane)[a]	Dimethylamine	**19**/**20**	51/49	89
12	B	Aziridine	**5**/**6**	5/95	85
13	B	Piperidine	**9**/**10**	26/74	93
14	B	Dimethylamine	**11**/**12**	13/87	95
15	B	Ammonia	**13**/**14**	31/69	84
16	C	Aziridine	**5**/**6**	32/68	80
17	C	Piperidine	**9**/**10**	32/68	95
18	C	Dimethylamine	**11**/**12**	26/74	96
19	C	Ammonia	**13**/**14**	30/70	87

[a] Instead of 6,7-dichloroquinoline-5,8-dione, 6,7-dibromo-2-methylquinoline-5,8-dione[9] was used.
[b] Analyzed by ^{1}H NMR.
[c] Isolated by column chromatography.

Acknowledgements

This work was supported by a grant from the Good Health R&D Project, Korean Ministry of Health and Welfare through a Research Fund (No. 96-D-1-0009 and 97-M-2-0037).

References

1. (a) Lown, J. W.; Sim, S.-K. *Can. J. Chem.* **1976**, *54*, 2563. (b) Porter, T. H.; Bowman, C. M.; Folkers, K. *J. Med. Chem.* **1973**, *16*, 115. (c) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918. (d) Shaikh, I. A.; Johnson, F.; Grollman, A. P. *J. Med. Chem.* **1986**, *29*, 1329. (e) Ryu, C. K.; Kim, H. J. *Arch. Pharm. Res.* **1994**, *17*, 139. (f) Wan, Y.-P.; Porter, T. H.; Folkers, K. *J. Heterocycl. Chem.* **1974**, *17*, 139. (g) Take, Y.; Oogose, K.; Kubo, T.; Inouye, Y.; Nakamura, S. *J. Antibiot.* **1987**, *40*, 679.
2. Pratt, Y. T. *J. Org. Chem.* **1962**, *27*, 3905.
3. Yoshida, K.; Ishiguro, M.; Honda, H.; Yamamoto, M.; Kubo, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4335.
4. (a) Klimovich, O. S.; Boldyrev, B. G.; Kolesnikov, V. T. *Khim. Geterotsikl. Soedin.* **1975**, *11*, 1539. (b) Klimovich, O. S.; Kolesnikov, V. T.; Sazhnikov, V. A. *Zh. Prickl. Khim.* **1976**, *49*, 1823. (c) Klimovich, O. S.; Kolesnikov, V. T. *Visn. L'viv. Politekh. Inst.* **1977**, *112*, 39.
5. Selected data: Compound **5**: mp 170–171°C; ^{1}H NMR ($CDCl_3$): δ 8.91 (dd, 1, C2–H), 8.37 (dd, 1, C4–H), 7.62 (dd, 1, C3–H), 2.57 (s, 4, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 177.59, 176.52, 154.14, 152.88, 146.63, 134.72, 128.78, 127.87, 126.23, 30.10; IR (KBr) 1692, 1664, 1590, 1556, 1474, 1290 cm^{-1}; anal. calcd for $C_{11}H_7ClN_2O_2$: C, 56.31;

H, 3.01; N, 11.94. Found: C, 56.62; H, 2.78; N, 11.49. Compound **6**: mp 171–172°C; ^{1}H NMR ($CDCl_3$): δ 8.93 (dd, 1, C2–H), 8.35 (dd, 1, C4–H), 7.62 (dd, 1, C3–H), 2.57 (s, 4, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 178.83, 175.82, 154.81, 151.77, 147.46, 134.74, 127.88, 127.84, 127.34, 30.04; IR (KBr) 1676, 1552, 1362, 1284 cm^{-1}; anal. calcd for $C_{11}H_7ClN_2O_2$: C, 56.31; H, 3.01; N, 11.94. Found: C, 56.57; H, 2.95; N, 11.64. Compound **7**: mp 166–167°C; ^{1}H NMR ($CDCl_3$): δ 8.94 (dd, 1, C2–H), 8.41 (dd, 1, C4–H), 7.63 (dd, 1, C3–H), 2.64 (s, 4, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 177.03, 176.46, 155.07, 154.07, 146.49, 134.96, 128.46, 127.78, 119.39, 30.67; IR (KBr) 1690, 1650, 1586, 1552, 1370, 1288 cm^{-1}; anal. calcd for $C_{11}H_7BrN_2O_2$: C, 47.34; H, 2.53; N, 10.04. Found: C, 47.28; H, 2.63; N, 10.11. Compound **8**: mp 166–167°C; ^{1}H NMR ($CDCl_3$): δ 8.97 (dd, 1, C2–H), 8.37 (dd, 1, C4–H), 7.63 (dd, 1, C3–H), 2.62 (s, 4, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 178.83, 175.69, 154.68, 153.93, 147.11, 134.75, 127.63, 127.16, 121.21, 30.55; IR (KBr) 1672, 1546, 1354, 1276 cm^{-1}; anal. calcd for $C_{11}H_7BrN_2O_2$: C, 47.34; H, 2.53; N, 10.04. Found: C, 47.37; H, 2.52; N, 10.11.

6. Crystal data: single crystals (crystal size: 0.35×0.35×0.1 mm) of **8** are monoclinic at 293 K, space group, $P2_1/a$ with $a=7.500(3)$ Å, $\alpha=90°$, $b=15.645(3)$ Å, $\beta=110.38(2)°$, $c=9.138$ Å, $\gamma=90°$ and $Z=4$ ($D_{calcd}=1.844$ g cm^{-3}; absorption coefficient = 40.73 cm^{-1}). A total 1438 independent data were collected (θ range for collection: 2.38–24.96°; completeness to $2\theta=24.96$: 72.9%; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 1.097; final R indices [$I>2\sigma(I)$]: $R_1=0.0632$, $wR_2=0.1587$; R indices (all data): $R_1=0.0652$, $wR_2=0.1631$; Largest difference peak and hole: 1.212 and −1.575 e Å^{-3}).
7. Selected data: Compound **15**: mp 182–183°C; ^{1}H NMR ($CDCl_3$): δ 8.34 (d, 1, C4–H), 7.50 (d, 1, C3–H), 2.76 (s, 3, CH_3), 2.64 (s, 4, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 177.20, 176.46, 164.27, 154.80, 145.85, 134.95, 127.64, 126.19, 119.12, 30.55, 24.93; IR (KBr) 1686, 1648, 1596, 1550, 1368, 1280 cm^{-1}; anal. calcd for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.09; N, 9.56. Found: C, 49.20; H, 2.97; N, 9.57. Compound **16**: mp 173–174°C; ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 1, C4–H), 7.43 (d, 1, C3–H), 2.70 (s, 3, CH_3), 2.58 (s, 4, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 178.26, 175.83, 165.11, 153.67, 146.55, 134.74, 127.00, 125.36, 120.71, 30.44, 25.16; IR (KBr) 1678, 1566, 1457, 1358, 1278 cm^{-1}; anal. calcd for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.09; N, 9.56. Found: C, 49.15; H, 3.13; N, 9.59.
8. Patai, S. In *The Chemistry of Functional Groups*; Berger, S. T.; Rieker, A., Eds. The chemistry of the quinoid compound. John Wiley: Bristol, 1974; Vol. 1, p. 187.
9. Choi, H. Y.; Lee, B. S.; Chi, D. Y.; Kim, D. J. *Heterocycles* **1998**, *48*, 2647.
10. Lee, K. C.; Chi, D. Y. *J. Org. Chem.* **1999**, *64*, 8576.