Effects of a 2-Substituent on the Ratio of *N*- and *O*-Alkylation of 4(3*H*)-Quinazolinones[1)]

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Alkylation of 4(3*H*)-quinazolinones with 1-iodopentane in the presence of sodium hydride gave a mixture of 3-pentyl-4(3*H*)-quinazolinones (2) and 4-pentyloxyquinazolines (3). The ratio of *O*-alkyl/*N*-alkyl products varied according to the 2-substituents of the quinazoline ring. Multiple regression analyses revealed that the ratio was determined by a steric factor (width parameter of *B*) and an electronic factor (in terms of Hammett's σ_p) of the 2-substituent. It was found to be the case in the reported alkylation of 4(3*H*)-quinazolinones with propargyl bromide.

Keywords *O*-alkylation; *N*-alkylation; 4(3*H*)-quinazolinone; multiple regression analysis; Verloop's STERIMOL parameter; electronic parameter

It is known that 4(3*H*)-quinazolinones react normally with alkyl halide at the 3-nitrogen atom of the quinazoline ring and occasionally at the oxygen atom.[2)] However, the reason the product ratio varies in the alkylation has remained unclear.

In the previous paper, we reported the syntheses and nootropic properties of 4-alkoxyquinazolines, and described that the alkylation of 2-(4-piperidyl)-4(3*H*)-quinazolinone (**1a**) and 2-(1-piperazinyl)-4(3*H*)-quinazolinone (**1b**) with 1-iodopentane gave differently pentylated products: although **1a** gave a mixture of 3-pentyl-4(3*H*)-quinazolinone (**2a**) and 4-pentyloxyquinazoline (**3a**), **1b** gave 4-pentyloxyquinazoline (**3b**) as a sole product.[1)]

Similar results were reported by Bogentoft and coworkers: the alkylation of 4(3*H*)-quinazolinones (**1**) with propargyl bromide gave a mixture of 3-propargyl-4(3*H*)-quinazolinones (**4**) and 4-propargyloxyquinazolines (**5**). (See Table IV)[3)] As for the ratio of **4** to **5**, Bogentoft *et al.* presumed that a steric hindrance of 2-substituents of the quinazoline ring facilitated the 4-*O*-alkylation; however, their presumption did not always seem to be correct. For example, they adopted large steric hindrance to explain the selective 4-*O*-alkylation of 2-CF_3 derivative (**1f**) in spite of a small molecular volume of the CF_3 group.

Also, in our case, despite the similarity of piperidyl and piperazinyl groups in terms of shape, the ratio of **2** to **3** was quite different, as described above. Therefore, the ratio of **2** to **3** is not explicable by a steric hindrance of the 2-substituents alone. Other factors such as electronic effects should be considered.

The purpose of this work is to quantitatively study the influences of various 2-substituents of the quinazoline ring on the ratio of 3-*N*- and 4-*O*-alkylated products in the alkylation of 4(3*H*)-quinazolinones.

Experimental

Melting points were measured with a capillary melting point apparatus (Yamato MP-21) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-50 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a Hitachi R-24B NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; m, multiplet. Elemental analyses were performed by the Analytical Department of Kanebo Research Center. HPLC was performed on a Shimadzu LC-6A apparatus equipped with an Inertsil ODS column (4.6 × 250 mm, Gasukuro Kogyo). Thin-layer chromatography (TLC) was performed on Merck precoated Silicagel $60F_{254}$ plates. For column chromatography, Merck Silica gel 60 was used.

Alkylation of 2-Isopropyl-4(3*H*)-quinazolinone (1d) NaH (60% in oil) (0.5 g, 12 mmol) was added to a mixture of **1d** (1.7 g, 9.0 mmol), 1-iodopentane (1.9 g, 9.6 mmol) and *N*,*N*-dimethylformamide (25 ml) at 0 °C, and the mixture was stirred at 70 °C for 2 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–AcOEt (8 : 1) to give **2d** (0.4 g, 17%) as a colorless oil and **3d** (1.2 g, 52%) as a colorless oil. **2d**; IR (neat): 1680, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, $J=6$ Hz), 1.2—2.0 (6H), 1.50 (6H, d, $J=6$ Hz), 3.15 (1H, m), 4.15 (2H, t, $J=7$ Hz, N-C$\underline{H}_2$-), 7.2—8.4 (4H). *Anal.* Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.21; H, 8.64; N, 10.76. **3d**: ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, $J=6$ Hz), 1.3—2.2 (6H), 1.40 (6H, d, $J=6$ Hz), 3.21 (1H, m), 4.58 (2H, t, $J=6$ Hz, O-C$\underline{H}_2$-), 7.2—8.3 (4H). *Anal.* Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.37; H, 8.66; N, 10.78.

Pentylation of the other 4(3*H*)-quinazolinones was similarly performed, and the results are listed in Table I. In order to confirm the reproducibility of the product ratio, we repeated the reaction of **1d**, and used HPLC analysis (mobile phase, MeOH; detection, 254 nm) to find that the ratio of **2d** : **3d** was 30 : 70, which agreed with that of the isolated yield. Although HPLC analysis is useful for the determination of the product ratio, it requires isolated authentic samples and their relative UV absorption intensities at a given wave length. In our case, the product ratio analyzed by the HPLC method agreed with the isolated yield ratio, and we used the latter in subsequent analyses.

It is important to explain material balance in a quantitative analysis. In the case of **1a**, the reaction was uncompleted, and 46% of the starting material was recovered. Similarly, starting material was detected by TLC in the cases of **1c**, **1d**, **1f** and **1g**.

Results and Discussion

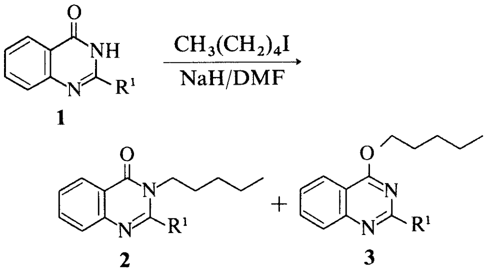
Table I shows that the 2-H derivative (**1c**) reacted with 1-iodopentane to give 3-pentyl-4(3*H*)-quinazolinone (**2c**) selectively, the 2-isopropyl derivative (**1d**) gave a mixture of 3-*N*- and 4-*O*-pentylated products (**2d** and **3d**), and the 2-*tert*-butyl derivative (**1e**) gave 4-pentyloxyquinazoline (**3e**) selectively. It is probable that steric hindrance of the 2-substituent facilitates the 4-*O*-alkylation. However, the 2-(*N*,*N*-dimethylamino) derivative (**1i**) selectively gave 4-pentyloxyquinazoline (**3i**) in spite of the sterical similarity between the *N*,*N*-dimethylamino and isopropyl groups. Similar relations were seen in the case of **1a** and **1b**. Moreover, the 2-CF_3 derivative (**1f**) selectively gave 4-pentyloxyquinazoline (**3f**). The CF_3 group is sterically smaller than the isopropyl group, judging from their steric parameter values such as molar refraction or van der Waals volume.[4]

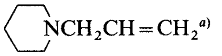
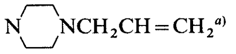
In order to investigate the influences of the 2-substituent on the ratio of the pentylated products, quantitative analyses using traditional extrathermodynamic parameters and Verloop's STERIMOL parameters[5] were performed, and Eq. 1 was obtained as the best equation.

$$\log O\text{-alkyl}/N\text{-alkyl} = 2.13(\pm 1.25)\sigma_p + 3.35(\pm 0.80)B - 5.86(\pm 1.55) \qquad (1)$$

$$n=10,\quad r=0.968,\quad s=0.525,\quad F=52.6$$

TABLE I. Ratio of 3-*N*- and 4-*O*-Pentylated Products (**2** and **3**)



No.	Starting materials (**1**) R^1	Ratio (Isolated yield %)	
		2	**3**
a	 NCH$_2$CH=CH$_2$[a]	25 (6)	75 (18)
b	 N NCH$_2$CH=CH$_2$[a]	0	100 (86)
c	H	100 (60)	0
d	CH(CH$_3$)$_2$	25 (17)	75 (52)
e	C(CH$_3$)$_3$	0	100 (88)
f	CF$_3$	0	100 (50)
g	 CH$_2$N NCH$_3$	87 (33)	13 (5)
h	N(CH$_3$)$_2$	0	100 (74)
i	N(CH$_3$)Ph	6 (5)	94 (80)
j	O(CH$_2$)$_4$CH$_3$	100 (77)	0

a) Reference 1.

In Eq. 1 and the following equations, the numbers in parentheses are the 95% confidence intervals, n is the number of data points used in deriving the equation, r is the multiple correlation coefficient, s is the standard deviation, and F is the F-ratio between the variances in the calculated and observed ratios.

In Eq. 1, *O*-alkyl/*N*-alkyl is the ratio between the 4-*O*- and 3-*N*-alkylated products.[6] When the 4-*O*-pentylation or 3-*N*-pentylation selectively occurred, the log *O*-alkyl/*N*-alkyl value can not be calculated. In such cases, considering measuring error, we regarded its selectivity as 99.5%, and the log *O*-alkyl/*N*-alkyl was calculated to be 2.30 or −2.30, respectively. σ_p is Hammett's electronic parameter of the 2-substituent. In the case of 3-*N*-alkylation, as its reactive site is located at the *ortho* position of the substituent, the use of σ_p is unquestionable. In the case of 4-*O*-alkylation, on the other hand, its reactive 4-oxygen atom is located at the *meta* position of the substituent, so σ_m seemed to be more suitable than σ_p. However, it was reported that the adoption of σ_p or σ_m in heterocyclic compounds depended on whether or not an electron resonance effect was involved.[7] In our case, a resonance effect is recognized, as shown in Chart 1, and we adopted σ_p in this analysis. B represents the width parameter of the 2-substituent in the direction to the 3-position of the quinazoline ring. In determining the B value, we assumed the conformation of a 2-substituent as follows. Alkyl groups can freely rotate, and the smallest width B_1 was adopted as B for the alkyl groups. In the case of amino and alkoxy groups, conjugation of the lone pair electron with the quinazoline ring restricts the conformation of these groups, and the largest width of B_4 would be located on the opposite side of the reactive

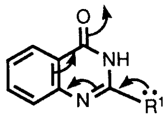


Chart 1

TABLE II. 3-Pentyl-4(3*H*)-quinazolinones (**2**) and 4-Pentyloxyquinazolines (**3**)

No.	^{1}H-NMR (CDCl$_3$) δ	IR cm^{-1} $\nu_{C=O}$	Formula	Analysis (%) Calcd (Found)		
				C	H	N
2c	0.90 (3H, t, *J*=6 Hz), 1.2—2.2 (6H), 3.97 (2H, t, *J*=7 Hz), 7.3—8.4 (5H)	1670	$C_{13}H_{16}N_2O$	72.19 (72.12	7.46 7.64	12.95 12.87)
2g	0.92 (3H, t, *J*=6 Hz), 1.1—2.1 (6H), 2.30 (3H, s), 2.4—2.8 (8H), 3.70 (2H, s), 4.35 (2H, t, *J*=8 Hz), 7.6—8.1 (4H)	1675	$C_{19}H_{28}N_4O$ $\cdot 1.5C_4H_4O_4$[a]	59.75 (59.58	6.82 6.83	11.15 11.24)
2i	0.80 (3H, t, *J*=6 Hz), 1.0—1.8 (6H), 3.45 (3H, s), 3.85 (2H, t, *J*=8 Hz), 6.9—8.4 (9H)	1690	$C_{20}H_{23}N_3O$	74.74 (74.68	7.21 7.22	13.07 13.16)
2j	0.91 (3H, t, *J*=6 Hz), 0.95 (3H, t, *J*=6 Hz), 1.2—2.2 (12H), 4.12 (2H, t, *J*=7 Hz), 4.50 (2H, t, *J*=6 Hz), 7.2—8.4 (4H)	1690	$C_{18}H_{26}N_2O_2$	71.49 (71.54	8.67 8.87	9.26 9.28)
3e	0.93 (3H, t, *J*=6 Hz), 1.2—2.1 (6H), 1.45 (9H, s), 4.63 (2H, t, *J*=6 Hz), 7.3—8.3 (4H)		$C_{17}H_{24}N_2O$	74.96 (75.09	8.88 9.04	10.28 9.89)
3f	0.95 (3H, t, *J*=6 Hz), 1.2—2.2 (6H), 4.65 (2H, t, *J*=6 Hz), 7.5—8.4 (4H)		$C_{14}H_{15}F_3N_2O$	59.15 (59.04	5.32 5.31	9.85 9.82)
3g	0.92 (3H, t, *J*=6 Hz), 1.1—2.1 (6H), 2.30 (3H, s), 2.4—2.8 (8H), 3.85 (2H, s), 4.59 (2H, t, *J*=7 Hz), 7.3—8.3 (4H)		$C_{19}H_{28}N_4O$ $\cdot 2C_4H_4O_4$[a]	57.85 (57.65	6.47 6.51	9.99 9.93)
3h	0.95 (3H, t, *J*=6 Hz), 1.3—2.2 (6H), 3.3 (6H, s), 4.53 (2H, t, *J*=6 Hz), 7.0—8.2 (4H)		$C_{15}H_{21}N_3O$	69.47 (69.45	8.16 8.04	16.20 16.11)
3i	0.90 (3H, t, *J*=6 Hz), 1.2—2.1 (6H), 3.65 (3H, s), 4.28 (2H, t, *J*=7 Hz), 7.0—8.1 (9H)		$C_{20}H_{23}N_3O$	74.74 (74.73	7.21 7.44	13.07 13.00)

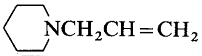
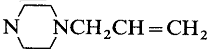
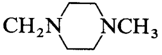
a) Fumarate.

3-nitrogen atom. Therefore, the second largest width (B_3) was adopted for the 1-piperazinyl, *N*,*N*-dimethylamino and *N*-methylanilino groups (**1b**, **1h** and **1i**), and B_1 for the pentyloxy group (**1j**). The results and parameters are listed in Table III.

The positive coefficient of B indicates that the substituent of a large B value facilitates the 4-*O*-alkylation. Similarly, the positive coefficient of σ_p indicates a facilitation of the 4-*O*-alkylation by a substituent of the electron withdrawing property.

In our reaction, because no other products by further reactions of **2** and/or **3** were observed, *O*-alkyl/*N*-alkyl reflects the ratio of the reaction rate. The Hammett equation correlating the rate constant (k) of a series of *para*- and *ortho*-substituted derivatives is usually expressed by Eq. 2 or Eq. 3.[8]

Table III. Parameters and Results of the Pentylation of 4(3*H*)-Quinazolinone

Compound		σ_p	B	log *O*-alkyl/*N*-alkyl	
No.	R^1			Found	Calcd
1a		$-0.15^{a)}$	$2.04^{a)}$	0.48	0.65
1b		$-0.83^{b)}$	$2.80^{b)}$	2.30	1.74
1c	H	0	1.00	−2.30	−2.51
1d	$CH(CH_3)_2$	−0.15	2.04	0.48	0.65
1e	$C(CH_3)_3$	−0.20	2.59	2.30	2.38
1f	CF_3	0.54	1.98	2.30	1.92
1g		$0.01^{c)}$	1.52	−0.83	−0.75
1h	$N(CH_3)_2$	−0.83	2.80	2.30	1.74
1i	$N(CH_3)Ph$	$-0.58^{d)}$	2.80	1.28	2.27
1j	$O(CH_2)_4CH_3$	−0.34	1.35	−2.30	−2.07

a) The values of the isopropyl group were adopted. *b*) The values of the *N*,*N*-dimethylamino group were adopted. *c*) The value of the *N*,*N*-dimethylaminomethyl group was adopted. *d*) The value was calculated as $\sigma_p[N(CH_3)Ph] = \sigma_p(NHPh) + \sigma_p(NHCH_3) - \sigma_p(NH_2)$.

$$\log k_{para} = \rho\sigma + C \qquad (2)$$

$$\log k_{ortho} = \rho'\sigma + \Sigma e_i E_i + C' \qquad (3)$$

In Eqs. 2 and 3, ρ is the reaction constant, C is a constant that corresponds to the $\log k$ value of unsubstituted compound, E_i is the free energy-related substituent parameter for component proximity effects, and e_i is the susceptibility constant. In our reaction, the 4-*O*-alkylation corresponds to the Hammett equation of a *para*-substituted derivative and the 3-*N*-alkylation to an *ortho*-substituted derivative. Therefore, the log *O*-alkyl/*N*-alkyl is shown as Eq. 4.

$$\begin{aligned}\log O\text{-alkyl}/N\text{-alkyl} &= \log k_{(O)} - \log k_{(N)} \\ &= (\rho_{(O)}\sigma_p + C_{(O)}) - (\rho_{(N)}\sigma_p + \Sigma e_i E_i + C_{(N)}) \\ &= (\rho_{(O)} - \rho_{(N)})\sigma_p - \Sigma e_i E_i + (C_{(O)} - C_{(N)}) \qquad (4)\end{aligned}$$

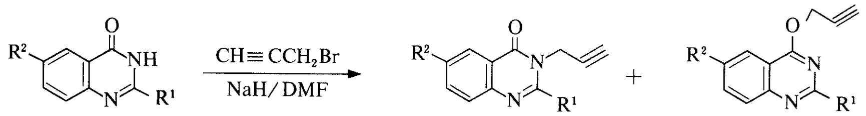
In Eq. 4, $k_{(O)}$ and $k_{(N)}$, $\rho_{(O)}$ and $\rho_{(N)}$ and $C_{(O)}$ and $C_{(N)}$ stand for rate constants, reaction constants and the constants of 4-*O*-alkylation and 3-*N*-alkylation, respectively. Since Eqs. 1 and 4 are the same form, it became clear that in our reaction, the free energy-related substituent parameter, E_i was replaced by B, and the values of $\rho_{(O)} - \rho_{(N)}$ and $C_{(O)} - C_{(N)}$ were calculated to be 2.13 and −5.86, respectively.

In order to confirm the validity of our analysis, we analyzed the result reported by Bogentoft and co-workers (Table IV), and obtained Eq. 5, which involves a statistically insignificant term.

$$\begin{aligned}\log O\text{-alkyl}/N\text{-alkyl} = {}& 3.33(\pm 3.77)\sigma_p + 1.25(\pm 0.99)B \\ & -3.41(\pm 2.62) \qquad (5)\end{aligned}$$

$$n = 16, \quad r = 0.719, \quad s = 1.24, \quad F = 6.97$$

Table IV. Ratio of 3-*N*- and 4-*O*-Propargylated Products (**4** and **5**)



1 **4** **5**

No.	Starting materials		Alkylated products		Parameters		log *O*-alkyl/*N*-alkyl	
	R^1	R^2	**4**	**5**	$\sigma_p{}^{a)}$	$B^{b)}$	Found	Calcd
1k	CH_2CH_3	H	100	0	−0.15	1.52	−2.30	−2.48
1l	$(CH_2)_3CH_3$	H	100	0	−0.16	1.52	−2.30	−2.50
1e	$C(CH_3)_3$	H	0	100	−0.20	2.59	2.30	1.16
1m	CH_2Ph	H	100	0	−0.09	1.52	−2.30	−2.31
1n	CH_2CH_2Ph	H	100	0	−0.12	1.52	−2.30	−2.40
1o	C_6H_{11}	H	90	10	−0.22	2.04	−0.95	−0.84
1f	CF_3	H	10	90	0.54	1.98	0.95	1.08
1p$^{c)}$	CH_2CH_3	NO_2	95	5				
1q	Ph	H	36	64	−0.01	$2.31^{d)}$	0.25	0.70
1r	*p*-NO_2–Ph	H	0	100	0.23	$2.31^{d)}$	2.30	1.37
1s	*p*-Cl–Ph	H	7	93	0.08	$2.31^{d)}$	1.12	0.95
1t	*m*-CH_3–Ph	H	46	54	0.01	$2.31^{d)}$	0.07	0.76
1u	*p*-CH_3–Ph	H	53	47	−0.07	$2.31^{d)}$	−0.05	0.53
1v	*0*-CH_3–Ph	H	100	0	−0.07	1.70	−2.30	−1.56
1w	*p*-CH_3O–Ph	H	64	36	−0.09	$2.31^{d)}$	−0.25	0.48
1x$^{c)}$	Ph	NO_2	0	100				
1y	2-Furyl	H	45	55	0.02	$2.31^{d)}$	0.09	0.78
1z	2-Thienyl	H	3	97	0.05	$2.31^{d)}$	1.51	0.87

a) Reference 4. *b*) Reference 5. *c*) Omitted from analysis. *d*) Calculated as $B = 3.11 \times \cos 42°$.

In this analysis, we omitted **1p** and **1x** because of a nitro group introduced to the quinazoline ring.

In Eq. 5, we used the B_3 value for the B of the benzene ring without any treatment. However, it was reported that biphenyl was twisting in a solution and in vapor phase; Bastiansen[9] reported the twisting angle in the vapor phase was 42° and Lunazzi[10] reported the twisting angle in a solution was similar to that in a vapor phase. It was presumable that 2-phenyl-4(3*H*)-quinazolinones might be similarly twisting, and the twisting angle should be considered in this analysis. We expected the twisting angle of **1q**—**1u** and **1w** should be 42°, so B was then calculated as $B_3 \times \cos 42° = 2.31$. Because **1v**, an *ortho* substituted derivative, should have a much larger steric hindrance than the others, we adopted 90° as the twisting angle and $B_1 = 1.70$ as the B value of **1v**. Reanalysis using these B values gave a statistically significant Eq. 6.

$$\log O\text{-alkyl}/N\text{-alkyl} = 2.75(\pm 1.93)\sigma_p + 3.68(\pm 1.00)B - 7.78(\pm 2.11) \qquad (6)$$

$$n=16, \quad r=0.933, \quad s=0.643, \quad F=43.6$$

The results and parameters are listed in Table IV.

In Eqs. 1 and 6, the coefficients of σ_p and B were statistically identical. Thus, we repeated our analysis using these two sets of data together and obtained Eq. 7.

$$\log O\text{-alkyl}/N\text{-alkyl} = 2.44(\pm 0.88)\sigma_p + 3.55(\pm 0.53)B + 1.32(\pm 0.53)D - 7.53(\pm 1.14) \qquad (7)$$

$$n=26, \quad r=0.950, \quad s=0.585, \quad F=67.7$$

In Eq. 7, the dummy variable (D) indicates the data set reported by Bogentoft ($D=0$) or by us ($D=1$). It is not clear how the dummy reflects the differences of the alkylating reagents and/or experimental conditions. However, it is confirmed that the ratio of alkylated products was affected by the width and electronic property of the 2-substituent of the quinazoline ring.

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