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Studies on Quinazolines. 11.† Intramolecular Imidate-Amide Rearrangement of 2-Substituted 4-(ω-Chloroalkoxy)quinazoline Derivatives. 1,3 -O → N Shift of Chloroalkyl Groups via Cyclic 1,3-Azaoxonium Intermediates

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Abstract: The ω-chloroalkylation of 2-substituted quinazolin-4(3*H*)-one derivatives **1** and **2** with Br-$(CH_2)_n$-Cl (n = 2−4) and the intramolecular imidate-amide rearrangement of the alkylated products are described. At room temperature, the 2-phenyl substituent promoted *O*-alkylation, whereas the less steric 2-benzyl group led to a higher ratio of *N*-alkylation. The investigation of the *O*-alkylated products, 4-ω-chloroalkoxyquinazolines, revealed that the migration of ω-chloroethyl and ω-chloropropyl groups from oxygen to nitrogen should be intramolecular via five- and six-membered cyclic 1,3-azaoxonium intermediates, respectively. Competition between rearrangement and nucleophilic substitution results in the formation of **7a**,**b** and **8a**,**b** from the nucleophilic substitution of **4a**,**b** and **6a**,**b**, respectively.

4(3*H*)-Quinazoline derivatives[1] possess a broad spectrum of biological activities such as antidiabetic,[2] anticonvulsant,[3] analgesic,[4] antibacterial,[5] protein tyrosine kinase inhibitors,[6] EGFR inhibitors,[7] PDGFR phosphorylation inhibitors,[8] CNS depressants,[9] and antitumor activity.[10] Furthermore, the heterocyclic core constitutes more than 40 alkaloids[11] isolated from natural products, and some show interesting biological profiles such as antimalarial[12] and diuretic[13] properties. In continuation of our studies on quinazoline derivatives as α1-adrenoceptors,[14] we designed and synthesized a series of 2-substituted 3-(4-arylpiperazinyl)alkylquinazolin-4(3*H*)-one derivatives.

There are numerous methods available for the synthesis of quinazolinones and their derivatives.[15] Reports on solid-phase synthesis of related quinazolinones[16] are an additional impetus to explore their multifaceted importance. We adapted the procedure of direct cyclocondensation dehydrogenation[17] of anthranilamide with benzoic anhydride and phenylacetyl chloride to prepare our starting materials, 2-phenyl- (**1**) and 2-benzylquinazolin-4(3*H*)-one (**2**), respectively.

For the preparation of our potential target compounds, first **1** was treated with ω-chloroethyl bromide in K_2CO_3/DMF at room temperature, but unexpectedly it only led to the *O*-alkylated product **4a** instead of our desired key intermediate **3a**. Nevertheless, when the reaction was carried out at higher temperature, it was found that the *N*-alkylated derivative **3a** was the only product. A perusal of literature indicated that the *N*-/*O*-alkylation of heterocyclic ambident nucleophiles has been broadly studied.[18] A percentage of about 35:65 for the *N*-/*O*-propargyl products of **1** and no *O*-alkylation for the corresponding 2-benzyl derivative (**2**) were reported by two independent groups.[19] To probe this matter, we carried out the

† For part 10, see ref 14a.

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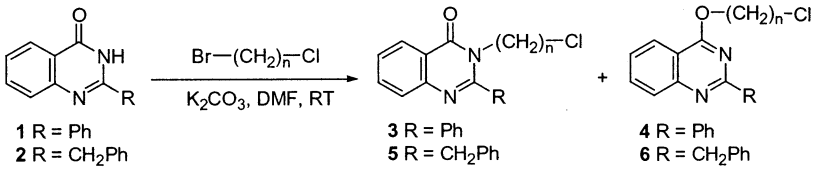
TABLE 1. *N*- and *O*-Alkylated Products of 2-Substituted Quinazolin-4(3*H*)-ones



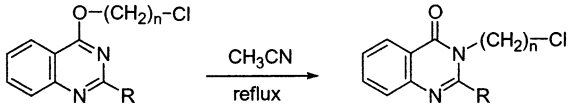
			% yield[a]				percentage	
no.	*n*	R	**3**	**4**	**5**	**6**	**3/4**	**5/6**
1a	2	Ph	2	77			3:97	
1b	3	Ph	2	86			2:98	
1c	4	Ph	0	82			0:100	
2a	2	CH_2Ph			72	4		95:5
2b	3	CH_2Ph			54	31		64:36
2c	4	CH_2Ph			49	32		60:40

[a] Yields are given for isolated, purified compounds.

alkylation of both **1** and **2** with a series of ω-chloroalkyl bromides (Br-$(CH_2)_n$-Cl, $n = 2-4$) in K_2CO_3/DMF at room temperature, which affords the *N*- and *O*-alkylated products in various yields as depicted in Table 1. Surprisingly, at room temperature the *O*-alkylation of **1** predominated over the *N*-alkylation in such a way that **4a**−**c** were the sole products with only a trace or even none of the *N*-alkylated products (**3a**−**c**). For the alkylation of **2**, 3-(ω-chloroethyl)quinazolin-4(3*H*)-one (**5a**) was indeed prevalent over the *O*-alkylated product **6a**. Nevertheless, the higher ω-chloroalkyl bromides led to an increasing amount of 4-alkoxyquinazoline derivatives (**6b**,**c**). Steric hindrance of the 2-substituents of quinazoline has been reasoned to hamper the *N*-alkylation.[19a] In addition, Hori and co-worker[20] asserted that both the steric and electronic factors of the 2-substituent should be involved in the determination of *N*-/*O*-alkylation of 4(3*H*)-quinazolinones. On the basis of our current results, the steric factor of the alkyl group apparently played a role in the competition of *N*- and *O*-alkylation. The structures of *N*- (**3**, **5**) and *O*-alkylated (**4**, **6**) derivatives could be distinguished conclusively by the ^1H and ^{13}C NMR and IR spectra. In the NMR spectra, the OCH_2 peaks in **4** and **6** are much more downfield compared to the corresponding peaks of NCH_2 in **3** and **5**. For instance, the OCH_2 of **4a** is 4.96 and 66.3 ppm in the ^1H and ^{13}C NMR, respectively, whereas the NCH_2 of **3a** is at 4.35 and 47.1 ppm, respectively. Furthermore, **3** and **5** showed strong peaks at about 1670 cm^{-1} indicating a C═O stretch of quinazolin-4(3*H*)-one.

Our preceding results showed that at room temperature the ω-chloroethylation of **1** only led to **4a**, whereas at higher temperature it led to the *N*-alkylated product **3a**. We assumed that a rearrangement might be involved in our case. A survey of literature indicated that aryl, alkyl, or allyl groups of imidates could migrate from oxygen to nitrogen.[21] The uncatalyzed thermal rearrangement of aryl imidates via 1,3-O → N shift, the so-called Chapman rearrangement, needed a temperature of over 200 °C. This degenerate rearrangement was also reported on the quinazoline system at a temperature of over 320 °C.[22] The rearrangement of alkyl imidates required even higher temperature than that in Chapman rearrangement, and its mechanism was proposed to be intermolecular.[23] Alkyl halides and Lewis acids were reported to catalyze the migration of alkyl groups.[24] Alternatively, 2-(ω-chloroethoxy)-1,3,5-trizaines[21] and 4-(ω-chloroethoxy)-2*H*-phthalazin-1-one[25] were reported to undergo uncatalyzed arrangement at temperatures of 110 and 153 °C, respectively. Both series of derivatives contain a ω-chloroethyl group, and they are analogous to our system. Therefore, we conducted the inspection on the rearrangement of 4-(ω-chloroalkoxy)quinazolines **4** and **6**.

TABLE 2. Rearrangement of 2-Substituted 4-(ω-Chloroalkoxy)quinazoline to 2-Substituted 3-(ω-Chloroalkyl)quinazolin-4(3*H*)-one



	n	R	time	conversion
4a → **3a**	2	Ph	24 h	100
4b → **3b**	3	Ph	7 d	100
4c → **3c**	4	Ph	*a*	0
6a → **5a**	2	CH_2Ph	18 h	100
6b → **5b**	3	CH_2Ph	5 d	100
6c → **5c**	4	CH_2Ph	*a*	0

[a] Long period.

Derivatives **4** and **6** were heated in CH_3CN at reflux to explore the possibility of rearrangement**,** and the results are depicted in Table 2. The 4-(ω-chloroethoxy)-quinazolines **4a** and **6a** were rearranged completely to the corresponding *N*-alkylated derivatives **3a** and **5a**, respectively, in less a day, and the 4-(ω-chloropropoxy)-

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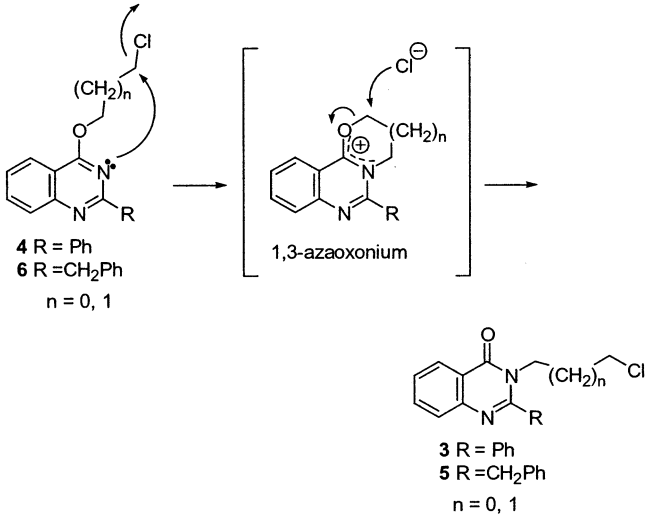
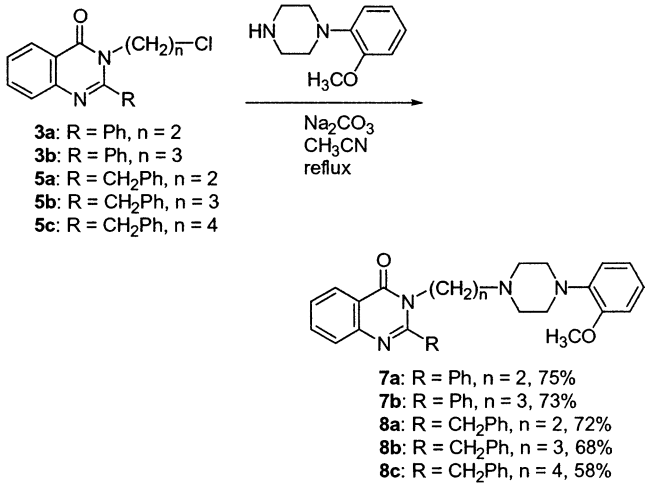
SCHEME 1



SCHEME 2



quinazolines **4b** and **6b** also accomplished the rearrangement to **3b** in 7 days and **5b** in 5 days, respectively. However, the rearrangement was not feasible for the 4-(*ω*-chlorobutoxy)quinazolines **4c** and **6c**, even after a prolonged period at reflux. Further, the rearrangements of **4c** and **6c** were examined in a higher boiling solvent, DMF, to see the achievability at higher temperature. In DMF, there was no reaction at 80 °C but there was decomposition to a complicated mixture without the expected rearranged product at 120 °C. In regard to 2-substituents, the 2-phenyl group prolonged the rearrangement in comparison to the 2-benzyl group, likely as a result of the steric hindrance. In addition, **4a** could also be rearranged completely to the corresponding **3a** at room temperature in 4 days. It appeared that higher temperature speeded up the rate of rearrangement, and our results were coherent with the reported result[25] in which the rearrangement was 85% completed in boiling DMF after 4 h.

Evidently, the low migration temperature of *ω*-chloroalkyl groups indicated that the mechanism should be different from those intermolecular rearrangements of alkyl groups. An intramolecular mechanism has been postulated on the basis of the rearrangement of *ω*-chloroethoxy-substituted 1,3,5-trizaines and 2*H*-phthalazin-1-one.[21,25] Our current results further ascertained the migration of *ω*-chloroalkyl groups being accomplished via an intramolecular mechanism since only *ω*-chloroethyl and *ω*-chloropropyl groups could migrate from oxygen to nitrogen rather than the *ω*-chlorobutyl group.

As illustrated in Scheme 1, the O → N shift of the chloroethyl and chloropropyl groups could proceed by an intramolecular two-step mechanism via the five- and six-membered cyclic 1,3-azaoxonium intermediates, respectively. Aubé et al.[26] have reported that a series of five- and six-membered 1,3-azaoxonium ions, also called iminium ethers, existed and could be isolated as tetrafluoroborate salts. The authors also reported that the structures of these iminium ethers have been characterized, and even the X-ray crystal structures have been solved.[26c] As a result of these stable 1,3-azaoxonium intermediates, the noncatalyzed intramolecular arrangements of *ω*-chloroethyl and *ω*-chloropropyl could be carried out at such low temperature. Obviously, the rearrangements of 4-(*ω*-chlorobutoxy)quinazolines **4c** and **6c** were hampered as a result of the restricted formation of a seven-membered cyclic intermediate. Our current results lend some support to the fact that the intramolecular two-step mechanism via the cyclic 1,3-azaoxonium intermediate for the O → N degenerate arrangement is involved in *ω*-chloroalkyl groups.

Although derivatives **4** and **6** were not our expected intermediates, all of the *ω*-chloroalkylated derivatives **3**−**6** were subjected to undergo nucleophilic substitution with 4-(2-methoxyphenyl)piperazine to provide the corresponding arylpiperazinyl-substituted quinazoline and quinazolinone derivatives. As expected, the nucleophilic substitution of **3** and **5** furnished the corresponding 3-[4-(2-methoxyphenyl)piperazin-1-yl]alkylquinazolin-4(3*H*)-ones **7** and **8**, respectively, in good yields (Scheme 2). To our surprise, the nucleophilic substitution of **4** and **6** under the same condition gave not only the nucleophilic substituted products **9** and **10**, respectively, but also **7** and **8**, respectively, which should come from **3** and **5** in different extent as can be seen in Table 3. The 4-(*ω*-chloroethoxy)quinazolines (**4a**, **6a**) exceptionally resulted in **7a** and **8a**, respectively, as the sole products in percentages of 88% and 100%, respectively. For the *ω*-chloropropoxyquinazolines (**4b**, **6b**), the direct substitution products (**9b**, **10b**) predominated over the rearranged products (**7b**, **8b**) resulting in ratios of 95:5 and 93:7, respectively. For the longer side chain *ω*-chlorobutoxy-substituted derivatives **4c** and **6c**, it led to only the direct substitution products **9c** and **10c**, respectively. Even after prolonged reflux, no rearranged product was found except for decomposition. It appears that the formation of **7** and **8** during the nucleophilic substitution of **4** and **6**, respectively, should result from the rearrangement of the *O*-alkylated derivatives to the more thermodynamic stable *N*-alkylated ones, then followed by the nucleophilic substitution.

Consequently, an intramolecular mechanism involving 1,3-azaoxonium clarified why the nucleophilic substitu-

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SCHEME 3

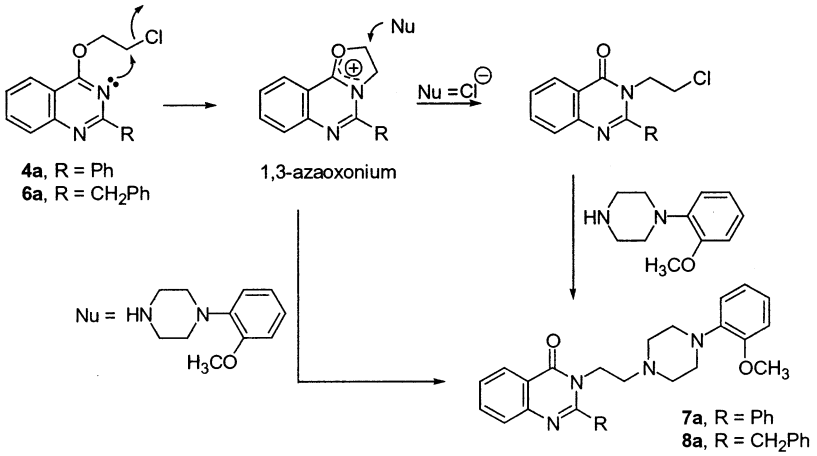
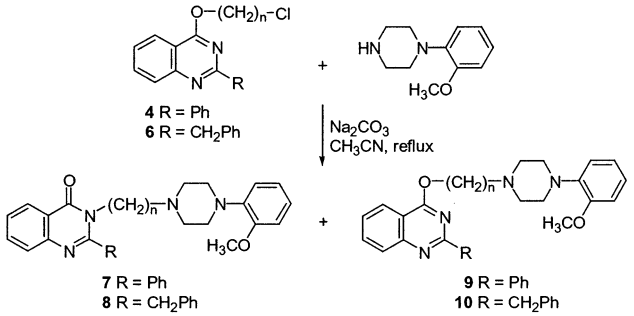


TABLE 3. ***N*- and *O*-[4-(2-Methoxyphenyl)piperazin-1-yl]alkyl Products from Nucleophilic Substitution of 2-Substituted 4-(*ω*-Chloroalkoxy)quinazolines**



			% yield[a]				percentage	
	n	R	**7**	**9**	**8**	**10**	**7/9**	**8/10**
4a	2	Ph	68	9			88:12	
4b	3	Ph	4	72			5:95	
4c	4	Ph	0	80[b]			0:100	
6a	2	CH_2Ph			74	0		100:0
6b	3	CH_2Ph			6	76		7:93
6c	4	CH_2Ph			0	74[b]		0:100

[a] Yields given for isolated, purified compounds. [b] Diisopropyl ethylamine was used. If Na_2CO_3 was used, the yields of **9c** and **10c** were 28% and 18%, respectively.

tion of **4** and **6** with arylpiperazine gave the direct substitution and arrangement products in different proportions (Table 3). It is the competing result of rearrangement and nucleophilic substitution. For the *ω*-chloroethyl derivatives **4a** and **6a**, the five-membered cyclic 1,3-azaoxonium intermediates were formed straightforwardly before the substitution took place. The distal end of the N−O tether could be attacked by either arylpiperazine directly or by chloride anion first and then substitution to provide **7a** and **8a** (Scheme 3). For the *ω*-chloropropyl derivatives **4b** and **6b**, the nuclophilic substitution took place before the formation of six-membered cyclic 1,3-azaoxonium intermediates, resulting the high ratio of **9b** and **10b**, respectively.

In summary, our current results provide further supports that the migration of both *ω*-chloroethyl and *ω*-chloropropyl groups from oxygen to nitrogen in imidate-amide rearrangement proceeds via an intramolecular mechanism involving cyclic 1,3-azaoxonium intermediates. Only five- and six-membered rings of 1,3-azaoxonium ions are feasible. Furthermore, the formation rate of a five-membered cyclic 1,3-azaoxonium ion is much faster than the reaction rate of nucleophilic substitution. On the other hand, the formation of a six-membered cyclic 1,3-azaoxonium ion is slower compared to the nucleophilic substitution.

Experimental Section

General Procedure for 3−6. To a stirred mixture of 2-substituted quinazoline **1** or **2** (4.5 mmol) and potassium carbonate (4.5 mmol) in DMF (10 mL) was added dropwise the appropriate bromochloroalkane (6.7 mmol) at room temperature for 24−48 h. The reaction was quenched by water (25 mL) and extracted with ethyl acetate (25 mL × 2). The combined organic extracts were washed with brine (25 mL × 3), dried by Na_2SO_4, and evaporated under reduced pressure. The residue was then purified by column chromatograph over silica gel eluting with ethyl acetate/hexane = 1/4.

General Procedure for 7−10. A mixture of appropriate alkylated product (1 mmol), Na_2CO_3 (2 mmol), and *N*-(2-methoxyphenyl)piperazine (2 mmol) was heated in dry CH_3CN (10 mL) at reflux for 24−48 h. The reaction mixture was then concentrated in vacuo, and the residue was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography over silica gel eluting with CH_2Cl_2/MeOH = 99/1 or ethyl acetate/hexane = 1/2.

Rearrangements of 4 and 6. A solution of **4** or **6** (1 mmol) in dry CH_3CN (10 mL) was heated at reflux for 2 h to 10 days, giving **3** or **5**, respectively, in quantitative yield. Analytically pure product was recrystallized from ethyl acetate/hexane.

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Supporting Information Available: Experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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