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Fused Pyrimidines. III.[1] The Reaction of 2,4-Dichloroquinazoline with *N*-Alkyl Cyclic Amines

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The reaction of 2,4-dichloroquinazoline with *N*-methylpyrrolidine gave *N*-(2-chloro-4-quinazolinyl)-*N*-methylpyrrolidinium chloride. This product, on being heated, gave 2-chloro-4-[*N*-(4-chlorobutyl)-*N*-methylamino]-quinazoline and it reacted with water in the presence of excess *N*-methylpyrrolidine to give a stable betaine, 4-(1-methyl-1-pyrrolidinio)-2-quinazolinolate.

By using this reaction, several new 4-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-2-chloroquinazoline derivatives were prepared from 2,4-dichloroquinazoline and *N*-alkyl cyclic amines.

Keywords——*N*-alkyl cyclic amine; pyrrolidine; piperidine; 2,4-dichloroquinazoline; amination; 4-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-2-chloroquinazoline; ^{13}C-NMR

In the preceding papers,[1] one of the authors has reported that 2,4(1*H*, 3*H*)-quinazolinedione (**1**) readily undergoes a von Braun-type reaction[2] with *N*-alkyl cyclic amines (**2**) in phosphoryl chloride through the formation of 4-oxo-3,4-dihydro-2-quinazolinyl dichlorophosphate and *N*-(4-oxo-3,4-dihydro-2-quinazolinyl)-*N*-alkyl cyclic ammonium chloride in sequence, to give 2-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-4-chloroquinazolines (**3**).

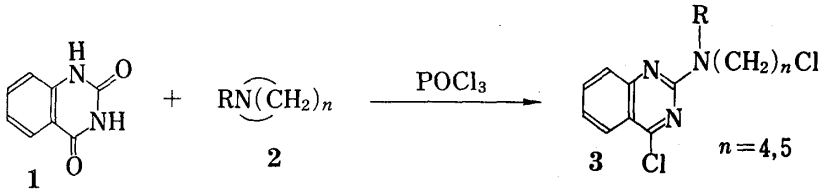

Chart 1

To extend the scope of these reactions, compound **2** was used as a nucleophile, in an attempt to convert the chlorine at the 4-position in 2,4-dichloroquinazoline (**4**) to an *N*-alkyl-*N*-(ω-chloroalkyl)amino group and to prepare 4-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-2-chloroquinazoline, which is anisomer of **3**, in a one-pot selective reaction.

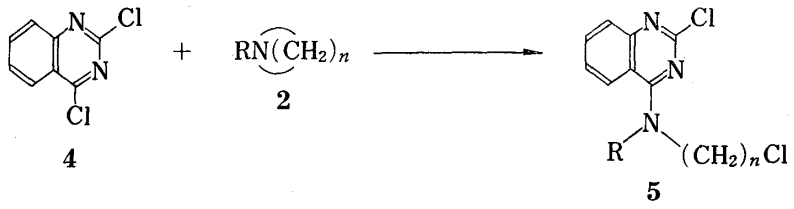

Chart 2

In the hope of obtaining 4-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-2-chloroquinazoline, **4** was allowed to react with 4 molar equivalents of *N*-methylpyrrolidine (**2a**) in acetone. However, the product obtained was not 2-chloro-4-[*N*-(4-chlorobutyl)-*N*-methylamino]-quinazoline (**5a**), but *N*-(2-chloro-4-quinazolinyl)-*N*-methylpyrrolidinium chloride (**6**), mp 88—90°C (dec.). When compound **6** was stirred at 95—100°C for 1 h, compound **5a**, mp 67—69°C, was obtained

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as colorless needles. The molecular formula of **5a** was determined as $C_{13}H_{15}ClN_3$ on the basis of its elemental analysis data and mass spectrum (MS) (M^+, *m/e*: 283, 285, 287; relative intensities 9: 6: 1). The relative intensities of the molecular ion peaks suggest the presence of two chlorine atoms in **5a**. The proton magnetic resonance (PMR) spectrum of **5a** indicates the presence of four methylene groups (δ: 1.50—2.31, 4H and 3.31—4.10, 4H), an *N*-methyl group δ: 3.38, 3H) and four aromatic protons (δ: 7.05—8.20). The ultraviolet (UV) spectrum of **5a** is quite similar to that of 2-chloro-4-(*N*-butyl-*N*-methylamino)quinazoline.[1b]

On the basis of these data, the structure of **5a** was established to be 2-chloro-4-[*N*-(4-chlorobutyl)-*N*-methylamino]-quinazoline, which is an isomer of 4-chloro-2-[*N*-(4-chlorobutyl)-*N*-methylamino]-quinazoline (**3a**).[1b]

Compound **6** was treated with water in the presence of excess *N*-methylpyrrolidine to give **7a** as colorless needles. The molecular formula of **7a** was determined as $C_{13}H_{15}N_3O$ on the basis of its elemental analysis data and MS (M^+, *m/e*: 229). Compound **7a** shows a characteristic PMR spectrum (in $CDCl_3$), which indicates the presence of an *N*-methylpyrrolidinium moiety (δ: 1.95—2.36, 3.26—3.67, 3.45, 4.69—5.06). On the other hand, the PMR spectral pattern observed in D_2O (δ: 1.60—2.35, 3.15—3.76, 3.25, 3.90—4.35 for *N*-methylpyrrolidinium moiety) is markedly different from that observed in $CDCl_3$. This suggests that compound **7a** is hydrated with D_2O. The infrared (IR) spectrum of **7a** indicates that it has no hydroxyl or carbonyl groups. On the basis of these data, the structure of **7a** was considered to be a betaine, 4-(1-methyl-1-pyrrolidinio)-2-quinazolinolate. 4-(1-Methyl-1-piperidinio)-2-quinazolinolate (**7h**) was also prepared from **4** and *N*-methylpiperidine (**2h**) in a similar manner.

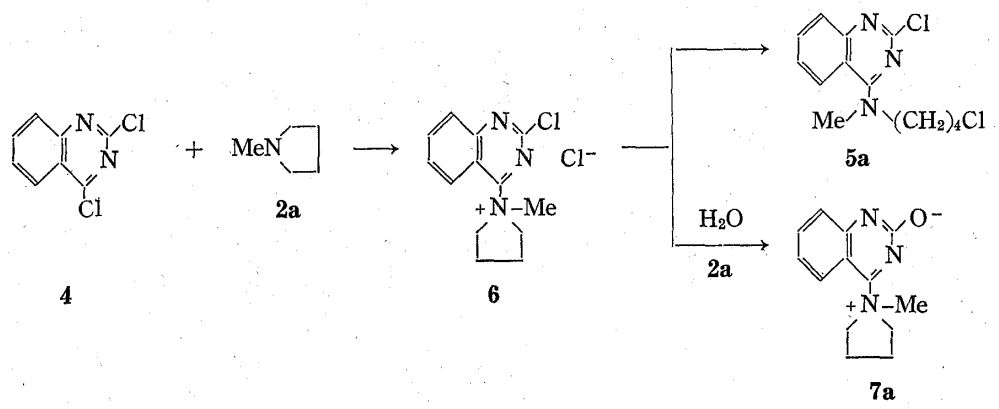

Chart 3

In order to confirm these structures, the PMR spectra of the compounds **7** (δ: N–CH_3, 3.45 for **7a** and 3.23 for **7h** in $CDCl_3$) were compared with that of 2-methoxy-4-(1-pyrrolidinyl)-quinazoline (**8**) (δ: 4.05 for O–CH_3 in $CDCl_3$), which was prepared from 2-chloro-4-(1-pyrrolidinyl)quinazoline[5] and sodium methylate.

The structures of **5a**, **7a** and **7h** are also supported by their ^{13}C-NMR spectra as described in the experimental section.

To clarify the relationship between **5a** and **3a**, the UV spectra of these compounds were compared. Compound **5a** shows a characteristic UV absorption maximum at 343 nm (Table III), while **3a** has an absorption maximum at 385 nm.[1b] By comparing their UV spectra in the region of about 300—400 nm, 4-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-2-chloroquinazoline (**5**) and its isomer, 2-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-4-chloroquinazoline (**3**) can be easily and unequivocally differentiated.

Then, compound **4** was allowed to react with *N*-ethylpyrrolidine (**2b**) under reaction conditions similar to those described for **6**. However, the product obtained was not *N*-(2-chloro-4-quinazolinyl)-*N*-ethylpyrrolidinium chloride, but a new compound. The molecular formula of this compound was determined to be $C_{14}H_{17}Cl_2N_3$ on the basis of its elemental

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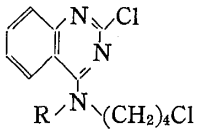
analysis data and MS (M^+, m/e: 297, 299, 301; relative intensities 9: 6: 1). The PMR spectrum of this compound indicates the presence of five methylene groups (δ: 1.30—2.42, 4H and 2.92—4.00, 6H), a methyl group (δ: 1.36, 3H) and four aromatic protons (δ: 6.91—8.01, 4H). On the basis of these data, the structure of this compound was concluded to be 2-chloro-4-[*N*-(4-chlorobutyl)-*N*-ethylamino]-quinazoline (**5b**).

To investigate further the scope and limitations of this type of reaction, the study was extended to include the use of other *N*-alkylpyrrolidines such as *N*-propyl- (**2c**), *N*-butyl- (**2d**), *N*-isobutyl- (**2e**), *N*-*sec*-butyl- (**2f**) and *N*-*tert*-butylpyrrolidine (**2g**). The results are summarized in Table I.

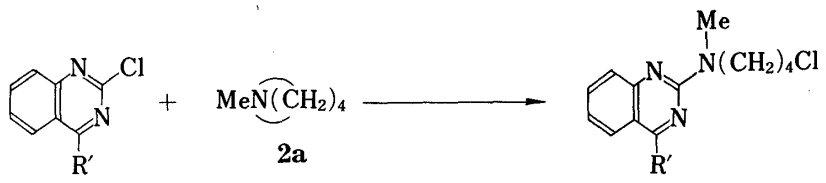
Table I. Yields (%) of **5** from the Reaction of **2** with **4**



5	R	Yield (%)	5	R	Yield (%)
5a	Me	67.0[a]	**5e**	isoBu	83.6
5b	Et	85.5	**5f**	*sec*-Bu	0
5c	Pr	89.0	**5g**	*tert*-Bu	0
5d	Bu	89.7			

a) Yield from **6**.

Similarly, heating 2-chloro-4-methoxyquinazoline[4] (**9a**) or 2-chloro-4-methylthioquinazoline[4] (**9b**) with **2a** in toluene afforded 2-[*N*-(4-chlorobutyl)-*N*-methylamino]-4-methoxyquinazoline (**10a**) and 2-[*N*-(4-chlorobutyl)-*N*-methylamino]-4-methylthioquinazoline (**10b**), respectively, in good yields. Their PMR spectral data are given in the experimental section.



9 **2a** **10a** : R′=OMe, **10b** : R′=SMe

Chart 4

From these results, it is apparent that the reaction of **4** with *N*-methylpyrrolidine (**2a**) produces a stable quaternary ammonium chloride (**6**), which is decomposed to give **5a** and which reacts with water in the presence of a base to give a stable betaine, 4-(1-methyl-1-pyrrolidinio)-2-quinazolinolate (**7a**). However, when a bulky amine, such as *N*-ethyl- (**2b**), *N*-propyl- (**2c**), *N*-butyl- (**2d**) or *N*-isobutylpyrrolidine (**2e**), is allowed to react with **4**, the quaternary ammonium salt formed is decomposed immediately to give 4-[*N*-alkyl-*N*-(4-chlorobutyl)amino]-2-chloroquinazoline (**5b**—**e**) in good yield. An even bulkier amine, such as *N*-*sec*-butyl- (**2f**) or *N*-*tert*-butylpyrrolidine (**2g**), cannot react further with **4**.

The introduction of an *N*-alkyl-*N*-(ω-chloroalkyl)amino group into other organic compounds by using this type of reaction is now under investigation and the results will be reported elsewhere.

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Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi EPI-G3 spectrophotometer, UV spectra were recorded with a Shimadzu UV-210 machine and MS were measured with a Hitachi RMS-4 mass spectrometer. PMR spectra were taken with a Hitachi R-24 spectrometer, and ^{13}C-NMR spectra were taken with a Varian XL-100A spectrometer; chemical shifts were expressed in ppm (δ) from tetramethylsilane as an internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Silica gel (Kiesel gel, Merck) was used for column chromatography.

Reaction of *N*-Methylpyrrolidine (2a) with 2,4-Dichloroquinazoline (4)——A mixture of **2a** (3.40 g) and **4** (2.00 g) in acetone (50 ml) was refluxed for 2 h. The reaction mixture was cooled to 0°C and the precipitates were collected by filtration and washed with acetone to give *N*-(2-chloro-4-quinazolinyl)-*N*-methylpyrrolidinium chloride (**6**) as a pale yellow crystalline powder, mp 88—90°C (dec.). 2.63 g (92.6%). *Anal.* Calcd for $C_{13}H_{15}Cl_2N_3$: C, 54.94; H, 5.32; N, 14.79. Found: C, 54.51; H, 5.52; N, 14.33. PMR (D_2O): 1.52—2.22 (4H, m, $CH_2\times2$), 3.42 (3H, s, CH_3), 3.58—4.55 (4H, m, $CH_2\times2$), 7.33—7.78 (3H, m, Ar–H), 7.96—8.21 (1H, m, Ar–H).

2-Chloro-4-[*N*-(4-chlorobutyl)-*N*-methylamino]-quinazoline (5a)——Compound **6** (1.00 g) was stirred at 95—100°C for 1 h, then dissolved in chloroform (5 ml) and subjected to column chromatography on silica gel. Elution with toluene gave 0.67 g (67.0%) of **5a** as colorless needles, mp 67—69°C. Its analytical data are listed in Tables II and III. ^{13}C-NMR ($CDCl_3$): 155.3 (s, C-2), 162.8 (s, C-4), 124.8 (d, C-5), 124.1 (d, C-6), 132.1 (d, C-7), 126.7 (d, C-8), 113.5 (s, C-4a), 152.6 (s, C-8a), 39.7 (q, N–CH_3), 51.6 (t, N–CH_2–), 23.8 (t, N–CH_2–CH_2–), 29.1 (t, N–CH_2–CH_2–), 44.0 (t, N–CH_2–).

Table II. Analysis Data for **5a—e**

Compound No.	R	mp (°C)	Molecular formula	Elemental analyses (%) Calcd (Found) C	H	N
5a	Me	67—69	$C_{13}H_{15}Cl_2N_3$	54.94 (55.06	5.32 5.60	14.79 14.98)
5b	Et	62—65	$C_{14}H_{17}Cl_2N_3$	56.38 (56.43	5.75 5.81	14.09 14.13)
5c	Pr	61—62	$C_{15}H_{19}Cl_2N_3$	57.70 (57.75	6.13 6.02	13.46 13.44)
5d	Bu	38—40	$C_{16}H_{21}Cl_2N_3$	58.90 (59.05	6.49 6.62	12.88 13.05)
5e	isoBu	48—50	$C_{16}H_{21}Cl_2N_3$	58.90 (58.80	6.49 6.32	12.88 12.67)

4-(1-Methyl-1-pyrrolidinio)-2-quinazolinolate (7a)——Compound **6** (1.00 g) was allowed to react with water (1 ml) in the presence of **2a** (3.00 g) in acetonitrile (50 ml) at 25—30°C for 5 h. The resulting mixture was concentrated and the residue was recrystallized from acetonitrile to give 0.36 g (42.0%) of **7a** as colorless needles, mp 182°C. *Anal.* Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.06; H, 6.59; N, 18.17. PMR ($CDCl_3$): 1.95—2.36 (4H, m, $CH_2\times2$), 3.26—3.67 (2H, m, $CH\times2$), 3.45 (3H, s, CH_3), 4.69—5.06 (2H, m, $CH\times2$), 7.23—7.70 (3H, m, Ar–H), 8.20—8.38 (1H, br d, Ar–H). PMR (D_2O): 1.60—2.35 (4H, m, $CH_2\times2$), 3.15—3.76 (2H, m, $CH\times2$), 3.25 (3H, s, CH_3), 3.90—4.35 (2H, m, $CH\times2$), 7.00—7.40 (3H, m, Ar–H), 7.71—7.90 (1H, br d, Ar–H). MS (M^+) *m/e*: 229. ^{13}C-NMR ($CDCl_3$): 172.6 (s, C-2), 158.7 (s, C-4), 125.5 (d, C-5), 124.0 (d, C-6), 131.1 (d, C-7), 125.3 (d, C-8), 121.3 (s, C-4a), 149.2 (s, C-8a), 50.8 (q, N–CH_3), 62.4 (t, ), 21.4 (t, ).

4-(1-Methyl-1-piperidinio)-2-quinazolinolate (7h)——Compound **4** (2.00 g) was allowed to react with water (1 ml) in the presence of *N*-methylpiperidine (4.00 g) in acetonitrile (50 ml) at 25—30°C for 5 h. The resulting mixture was concentrated and the residue was subjected to silica gel column chromatography. Elution with hexane–acetone (2: 1) gave crystals, which were recrystallized from acetonitrile to give 0.26 g (10.7%) of **7h** as colorless needles, mp 178—179°C. *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.06; H, 7.36; N, 17.38. PMR ($CDCl_3$): 1.20—2.20 (6H, m, $CH_2\times3$), 2.95—3.52 (2H, m, $CH\times2$), 3.23 (3H, s, CH_3), 4.35—5.02 (2H, m, $CH\times2$), 7.32—7.81 (3H, m, Ar–H), 8.33—8.58 (1H, br d, Ar–H). MS (M^+) *m/e*: 243. ^{13}C-NMR ($CDCl_3$): 172.9 (s, C-2), 157.9 (s, C-4), 125.7 (d, C-5), 124.2 (d, C-6), 131.2 (d, C-7), 125.4 (d, C-8), 121.3 (s, C-4a), 149.6 (s, C-8a), 54.7 (q, N–CH_3), 59.7 (t, ), 21.1 (t, ), 20.4

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(t, ).

General Procedure for 5——A mixture of **4** (2.00 g) and 4 molar equivalents of **2** in acetone (50 ml) was refluxed for 2 h. Excess **2** and acetone were evaporated off *in vacuo*, and the residue was dissolved in chloroform (50 ml). The chloroform layer was washed with water and dried over magnesium sulfate. The chloroform solution was concentrated to give a pale yellow oil, which was subjected to silica gel column chromatography. Elution with toluene gave 4-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-2-chloroquinazolines (**5**). The results are summarized in Tables II and III.

Table III. MS, UV and PMR Data for **5a—e**

Compound No.	MS (M^+) *m/e*	UV nm (ε_{max}) in EtOH	PMR δ: ppm in $CDCl_3$
5a	283, 285, 287	215(34000), 295(8700), 327(10100), 343(8100)	1.50—2.31 (4H, m, $CH_2\times2$), 3.31—4.10 (4H, m, $CH_2\times2$), 3.38 (3H, s, CH_3), 7.05—8.20 (4H, m, ph-H)
5b	297, 299, 301	215(34300), 296(8700), 329(10000), 343(8100)	1.30—2.42 (4H, m, $CH_2\times2$), 1.36 (3H, t, CH_3), 2.92—4.00 (6H, m, $CH_2\times3$), 6.91—8.01 (4H, m, ph-H)
5c	311, 313, 315	215(34700), 296(8500), 329(10100), 343(8300)	0.98 (3H, t, CH_3), 1.37—2.30 (6H, m, $CH_2\times3$), 3.15—3.92 (6H, m, $CH_2\times3$), 7.04—7.85 (4H, m, ph-H)
5d	325, 327, 329	215(34400), 296(8400), 329(10000), 343(8200)	0.95 (3H, m, CH_3), 1.11—2.51 (8H, m, $CH_2\times4$), 3.12—4.21 (6H, m, $CH_2\times3$), 6.94—8.02 (4H, m, ph-H)
5e	325, 327, 329	215(34400), 296(7800), 330(9800), 343(8300)	0.88 (6H, d, $CH_3\times2$), 1.29—2.45 (5H, m, $CH_2\times2$ and CH), 3.36 (2H, t, CH_2), 3.55 (2H, d, CH_2), 3.76 (2H, t, CH_2), 7.15—8.06 (4H, m, ph-H).

2-Methoxy-4-(1-pyrrolidinyl)quinazoline (8)——A solution of sodium methylate (0.60 g) in methanol (10 ml) was added to a solution of 2-chloro-4-(1-pyrrolidinyl)quinazoline[3] (2.34 g) in dimethylformamide (30 ml) at 25—30°C. The reaction mixture was stirred at 80—85°C for 2 h. The resulting mixture was concentrated *in vacuo* to dryness. The residue was washed with water and recrystallized from acetonitrile to give 1.63 g (73.3%) of **8** as colorless needles, mp 99—100°C. *Anal.* Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.98; H, 7.00; N, 18.56. PMR (CCl_4): 1.65—2.37 (4H, m, $CH_2\times2$), 3.70—4.12 (4H, m, $CH_2\times2$), 4.05 (3H, s, CH_3), 7.08—7.90 (3H, m, ph-H), 8.05—8.27 (1H, br d, ph-H).

2-[*N*-(4-Chlorobutyl)-*N*-methylamino]-4-methoxyquinazoline (10a)——A mixture of 2-chloro-4-methoxyquinazoline[4] (1.95 g) and **2a** (3.40 g) in toluene (50 ml) was refluxed for 4 h. The resulting mixture was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel. Elution with toluene gave 2.50 g (89.3%) of **10a** as a colorless oil. *Anal.* Calcd for $C_{14}H_{18}ClN_3O$: C, 60.10; H, 6.49; N, 15.02. Found: C, 60.07; H, 6.38; N, 14.55. PMR (CCl_4): 1.51—2.10 (4H, m, $CH_2\times2$), 3.22 (3H, s, CH_3), 3.40—3.90 (4H, m, $CH_2\times2$), 4.09 (3H, s, CH_3), 6.91—7.25 (1H, m, ph-H), 7.48—7.67 (2H, br s, ph-H), 7.81—8.08 (1H, br d, ph-H).

2-[*N*-(4-Chlorobutyl)-*N*-methylamino]-4-methylthioquinazoline (10b)——A mixture of 2-chloro-4-methylthioquinazoline[6] (2.10 g) and **2a** (3.40 g) in toluene (50 ml) was allowed to react and worked up as described for the preparation of **10a** to give 2.74 g (92.6%) of **10b** as a colorless oil. *Anal.* Calcd for $C_{14}H_{18}ClN_3S$: C, 56.84; H, 6.13; N, 14.21. Found: C, 56.96; H, 6.04; N, 14.28. PMR (CCl_4); 1.60—1.99 (4H, m, $CH_2\times2$), 2.60 (3H, s, CH_3), 3.24 (3H, s, CH_3), 3.35—4.00 (4H, m, $CH_2\times2$), 6.96—8.02 (4H, m, ph-H).

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