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Fused Pyrimidines. II.[1] Formation Mechanism of 2-[*N*-Alkyl-*N*-(ω-chloroalkyl)amino]-4-chloroquinazolines

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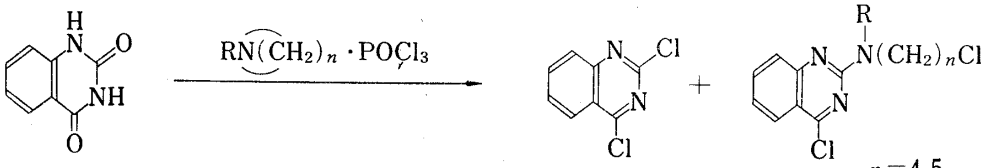
2,4(1*H*,3*H*)-Quinazolinedione readily undergoes a von Braun-type reaction with *N*-alkyl cyclic amines in phosphoryl chloride through the formation of 4-oxo-3,4-dihydroquinazolinyl dichlorophosphate and *N*-alkyl-*N*-(4-oxo-3,4-dihydro-2-quinazolinyl)cyclic ammonium chloride in sequence; the latter decomposes to give a new tertiary amine, 2-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-4-chloroquinazolines.

A possible reaction mechanism is discussed.

Keywords——2,4(1*H*,3*H*)-quinazolinedione; *N*-alkyl cyclic amine; 2,4-dichloroquinazoline; von Braun-reaction; dichlorophosphate; cyclic ammonium chloride; 2-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-4-chloroquinazoline; reaction mechanism

In the preceding paper,[1] the author has reported that in the reaction of 2,4(1*H*, 3*H*)-quinazolinedione (**1**) with phosphoryl chloride in the presence of excess *N*-alkyl cyclic amine, the hydroxyl groups at the 2- and 4-positions of the quinazoline nucleus are replaced by the *N*-alkyl-*N*-(ω-chloroalkyl)amino group and chlorine to give 2,4-dichloroquinazoline (**2**) and 2-[*N*-alkyl-*N*-(ω-chloroalkyl)amino]-4-chloroquinazoline (**3**), and the products ratio is markedly affected by the bulkiness rather than the basicity of the *N*-alkyl cyclic amine.



1 2 3

Chart 1

Formation of **3** is particularly interesting in the following respect: First, an alkylamino group is introduced at the 2-position of the quinazoline nucleus. Nucleophilic reactions at the 4-position proceed more rapidly than at the 2-position of **2**.[2] Secondly, an *N*-alkyl-*N*-(ω-chloroalkyl)amino group is introduced into the quinazoline nucleus in a one-pot reaction.

This report deals with the experimental results and presents a discussion on the formation mechanism of **3** from **1**.

Three routes (a, b and c) can be considered for the course of the reaction, involving three compounds, **2**, 2-chloro-4(3*H*)-quinazolinone (**4**) and 4-oxo-3,4-dihydro-2-quinazolinyl dichlorophosphate (**5**), as intermediates, respectively (Chart 2). The following investigation were undertaken to identify the actual intermediate.

Compound **2** was reacted with excess *N*-methylpyrrolidine in phosphoryl chloride, but **2**[3] was recovered.

When compound **4** synthesized by the method of Lange *et al.*[4] was reacted under similar conditions, compound **2** was the only product isolated, and the expected 4-chloro-2-[*N*-(4-chlorobuty-*N*-methylamino]quinazoline (**3a**) could not be detected.

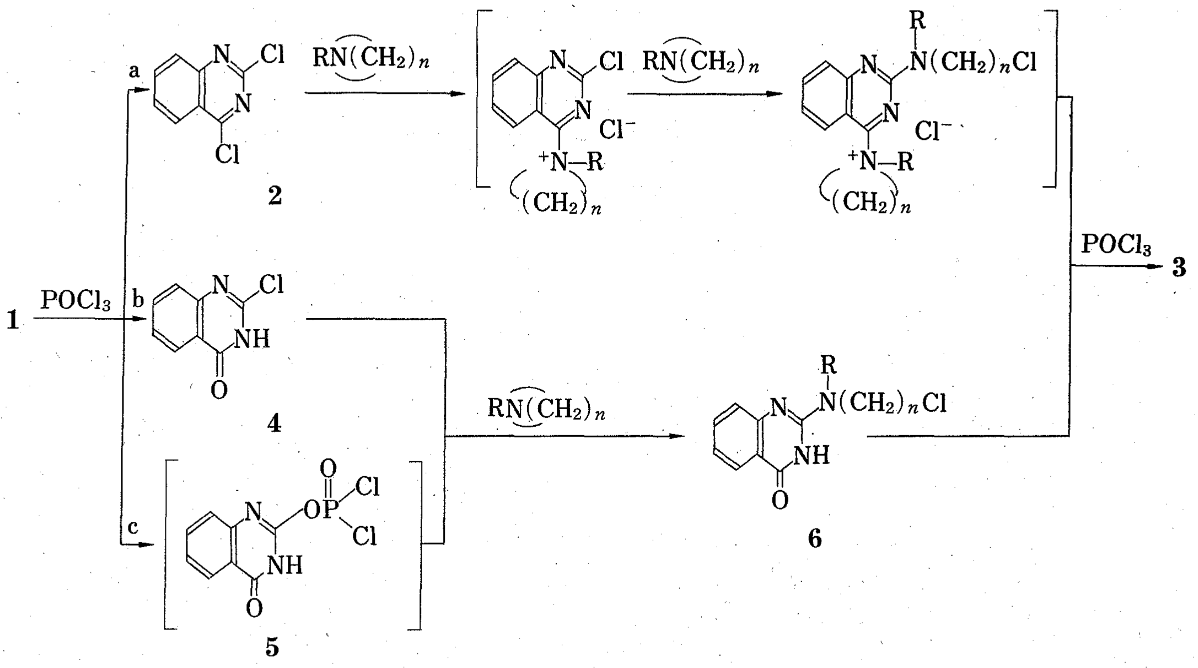


Chart 2

From these results, the involvement of **2** or **4** as an intermediate in the formation process of **3** was excluded.

N-Methylpyrrolidine was used as an acid binder in phosphoryl chloride in the chlorination of **1**, and the reaction was quenched in the course of chlorination. The products in the reaction mixture were examined by gas liquid chromatography to detect **1**, **2** and **3a**. From these data, it is suggested that the 4-hydroxyl group of **4** was smoothly replaced by chlorine to produce **2**, and compound **3a** was not produced at all.

Attempts to detect **5** were unsuccessful. However, when compound **1** was reacted with 1.1 mol equivalents of phosphoryl chloride in the presence of *N*-methylpyrrolidine, compound **6** was obtained as colorless needles, mp 152°C. The elemental analysis of **6** was in good agreement with the calculated value for $C_{13}H_{16}ClN_3O$, and the mass spectrum (M^+, *m/e*: 265, 267. relative intensities=3: 1). The relative intensities of molecular ion peaks suggested that **6** has one chlorine in the molecule. The proton magnetic resonance (PMR) spectrum of **6** indicated the presence of four methylene groups (δ: 1.49—2.21, 4H, m and 3.40—3.90, 4H, m), an *N*-methyl group (δ: 3.26, 3H, s), and four aromatic protons (δ: 7.05—8.32, 4H, m). The infrared (IR) absorptions at 3150 and 1670 cm^{-1} indicated the presence of an amide group.

On the basis of these data, the structure of **6** was assigned as 2-[*N*-(4-chlorobutyl-*N*-methylamino]-4(3*H*)-quinazolinone.

The chlorination of **6** with phosphoryl chloride in the presence or absence of *N*-methylpyrrolidine yielded **3a**. These results show that **5** and **6** may be involved as intermediates.

Consequently, the mechanism of the reaction of **1** with phosphoryl chloride in the presence of excess *N*-alkyl cyclic amine may be as shown in Chart 3.

It seems quite probable that the reaction proceeds initially through the formation of **5**, which may then be attacked by chloride anion or tertiary amine to give **4** and **7**, respectively.

i) When an alkylamine such as *N*-methyl-, *N*-ethyl-, *N*-propyl-, *N*-butylpyrrolidine or *N*-methylpiperidine[1] is used as a base in the chlorination of **1**, these amines react with 4-oxo-3,4-dihydro-2-quinazolinyl dichlorophosphate (**5**) to form *N*-alkyl-*N*-(4-oxo-3,4-dihydro-2-quinazolinyl)cyclic ammonium chloride (**7**). The intermediate **7** is converted to **6** *via* a von Braun-type reaction,[5] and the product is chlorinated to give **3**.

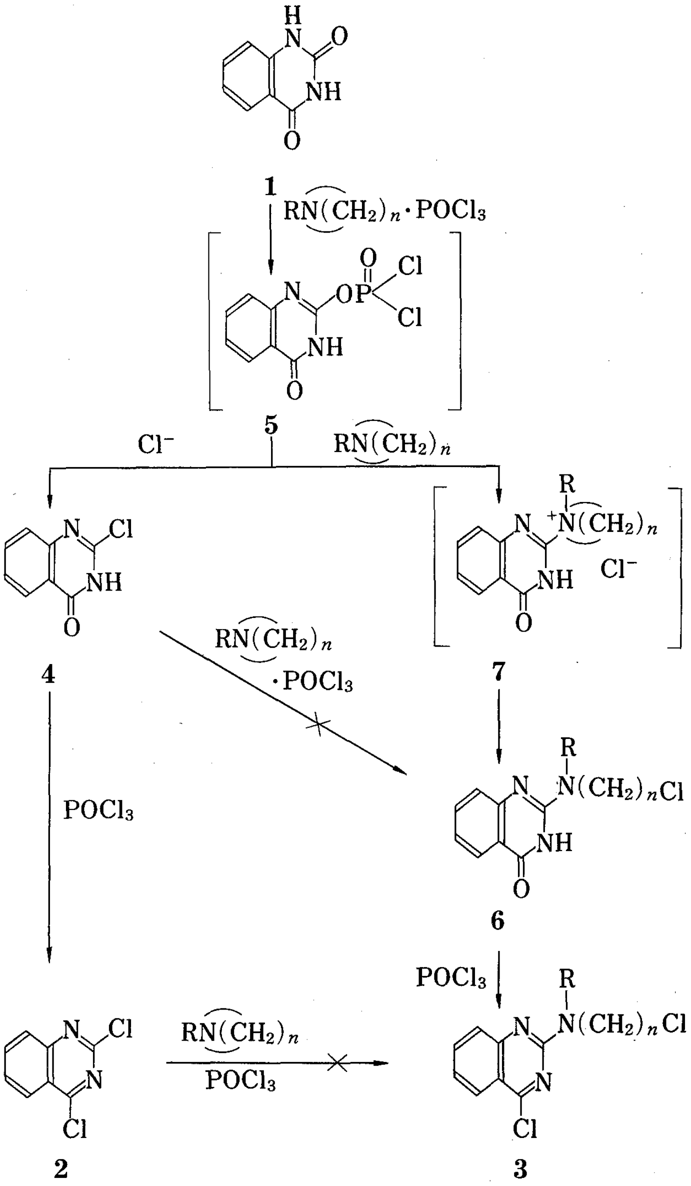


Chart 3

ii) When a bulky alkylamine such as *N*-*sec*-butyl-, *N*-*tert*-butylpyrrolidine or *N*-*sec*-butylpiperidine[1] is used as a base, the intermediate **5** cannot react with these amines and is attacked by a chloride anion to give **4**. Compound **4** is immediately converted to **2**, which does not react any further with the amines under these reaction conditions.

This mechanism can reasonably explain why the chlorination of **1** with phosphoryl chloride in the presence of triethylamine gives 4-chloro-2-diethylaminoquinazoline instead of **2**, while when tripropylamine is used as a base in place of triethylamine, compound **1** is smoothly converted to **2**.[6] This mechanism is comparable with the proposed mechanism for the reaction of phosphoryl chloride adducts of acid amide with amines to give amidines by nucleophilic attack.[7]

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded by using a Hitachi EPI-3 spectrophotometer and PMR spectra were taken with a Hitachi R-24 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. Gas liquid chromatography (GLC) was carried out on a Shimadzu GC-7AG gas chromatography with FID. Mass spectra (MS) were measured with a Hitachi RMS-4 mass spectrometer. The refractive index values were measured with an Erma refractometer.

2-Chloro-4(3*H*)-quinazolinone (4)——A mixture of 2,4-dichloroquinazoline (2) (2.0 g, 10 mmol) and sodium hydroxide aq. (10%, 50 ml) was stirred at 20—25°C for 5 h and the ice-cooled reaction mixture was adjusted with dil. hydrochloric acid (10%) at pH 6. The precipitates collected by filtration were washed with cold water to give a crystalline powder and recystallized from acetonitrile to give 1.2 g of **4** as colorless needles, mp 210—213°C (lit.,[2b] mp 213°C).

Reaction of 2 with *N*-Methylpyrrolidine in Phosphoryl Chloride——A mixture of **2** (1.0 g) and *N*-methylpyrrolidine (3 ml) in phosphoryl chloride (8 ml) was stirred at 20—25°C for 30 min. The reaction mixture was poured into ice-water to recover **2** quantitatively.

Reaction of 4 with *N*-Methylpyrrolidine in Phosphoryl Chloride——Compound **4** was reacted by a procedure similar to the described for the reaction of **2** with *N*-methylpyrrolidine to give **2**, mp 116—118°C (90%).

Chlorination of 1——*N*-Methylpyrrolidine (6 ml) was added to a mixture of **1** (1.6 g, 10 mmol) and phosphoryl chloride (15 ml) and the mixture was stirred at 20—25°C for 10 min. Excess phosphoryl chloride and *N*-methylpyrrolidine were evaporated off *in vacuo*, and the residue was dissolved in 20 ml of chloroform. Material insoluble in chloroform was removed by filtration. The filtrate was washed with water, satd. sodium bicarbonate aq., and water. After being dried over magnesium sulfate, the chloroform layer was concentrated to give 1.2 g of a yellow oil. The residue in toluene was examined by GLC to detect **1**, **2** and **3a**. GLC conditions: 1.5% silicon OV-17 on Gas chrom Q (80—100 mesh), 3 mm × 2 m; column temperature, 220°C; injection temperature, 280°C; carrier gas, N_2, 50 ml/min; t_R (min):

Compound	t_R	Yield (%)
2,4-Dichloroquinazoline	0'52"	12.7
2-Chloro-4(3*H*)-quinazolinone	0'81"	0
2,4-(1*H*, 3*H*)-Quinazolinedione	3'12"	9.8
4-Chloro-2-[*N*-(4-chlorobutyl)-*N*-methylamino]quinazoline	5'28"	70.5

The precipitate (0.4 g) was confirmed to be **1** by IR and PMR spectroscopy.

2-[*N*-(4-Chlorobutyl)-*N*-methylamino]-4(3*H*)-quinazolinone (6)——A mixture of **1** (3. 2g, 20 mmol), phosphoryl chloride (3.4 g, 22.2 mmol) and *N*-methylpyrrolidine (3.5 g, 41.2 mmol) in acetonitrile (300 ml) was stirred at 80—85°C for 8 h. The hot reaction mixture was filtered to recover unreacted **1** (1.8 g) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from acetonitrile to give 1.8 g of **6** (78.3%) as colorles needles.

Chlorination of 6——*N*-Methylpyrrolidine (6 ml) was added to a mixture of **6** (1.5 g) and phosphoryl chloride (15 ml) at 80—85°C. The mixture was stirred under the same conditions for 20 min. Excess phosphoryl chloride and *N*-methylpyrrolidine were evaporated off *in vacuo*, and the residue was dissolved in 20 ml of chloroform. The solution was washed with water, satd. $NaHCO_3$ aq. and water. After being dried over magnesium sulfate, the chloroform layer was concentrated to give 1.4 g of **3a** (87.5%) as a pale yellow oil, n_d^{20} 1.6147. The IR and PMR spectra of the product were identical with those of 4-chloro-2-[*N*-(4-chlorobutyl)-*N*-methylamino]quinazoline (**3a**) obtained directly from **1**.

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