FORMATION MECHANISM OF 2-(N-ALKYL-4-CHLOROBUTYLAMINO)-4-CHLORO-QUINAZOLINE

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Abstract —— The reaction of 2,4(1H,3H)-quinazolinedione (1) with N-alkylpyrrolidine in phosphoryl chloride undergoes readily the reaction of a von Braun type through the formation of dichlorophosphate and a quaternary ammonium salt in sequence, which decomposes to give 2-(N-alkyl-4-chlorobutylamino)-4-chloroquinazoline (3). A conceivable reaction mechanism is discussed.

In the preceding paper,[1] the author has reported that in the reaction of 1 with phosphoryl chloride in the presence of excess N-alkylpyrrolidine, the hydroxy groups of 2- and 4-position of quinazoline nucleus are replaced by the N-alkyl-4-chlorobutylamino group and the chlorine to give 2,4-dichloroquinazoline (2) and 3, and the products ratio is markedly affected by the bulkiness rather than the basicity of N-alkylpyrrolidine.

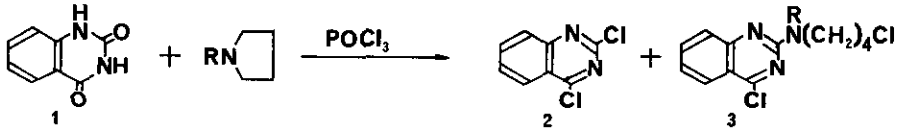

Chart 1

Formation of 3 is particularly interesting in the following respect: first, an alkylamino group is introduced to the 2-position of quinazoline nucleus. Nucleophilic reactions at the 4-position proceed more rapidly than at the 2-position of 2.[2,3] Secondary: an N-alkyl-4-chlorobutylamino group is introduced to quinazoline nucleus in a one-pot reaction.

This communication deals with experimental results and discussion on the formation mechanism of 3 from 1.

It was considered to involve one of three compounds, 2, 2-chloro-4(3H)-quina-

zolone (4) or dichlorophosphate (5), as an intermediate of this reaction. Following investigations were undertaken for obtaining information about the intermediate.

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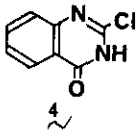

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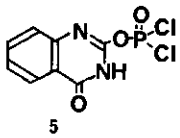

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Chart 2

Compound 2 was reacted with excess phosphoryl chloride in the presence of excess N-methylpyrrolidine, but 2 was recovered.[4]

When compound 4 synthesized by the method of Lange et al.[5] was worked up in a similar reaction condition, compound 2 was the only isolated product and the expected 4-chloro-2-(4-chloro-N-methylbutylamino)quinazoline (3a) could not detected.

From these results, the possiblities to involve 2 or 4 as an intermediate in the fromation process of 3 were excluded.

Any 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, 2-(4-chloro-N-methylbutylamino)-4(3H)-quinazolone (6) was obtained. 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 intermediate.

Consequently, a plausible mechanism for the reaction of 1 with phosphoryl chloride in the presence of excess N-alkylpyrrolidine is considered as shown in Chart 3.

It seems to be quite probable that the reaction proceeds initially through the formation of 5 and then it may be attacked by chloride anion or tertiary amine to give 4 and 7, respectively. i) When the alkylamine such as N-methyl-, N-ethyl-, N-propyl- or N-butylpyrrolidine[1] is used as a base in the chlorination of 1, this amine react with intermediate 5 to form quaternary ammonium salt 7. Intermediate 7 is converted to 6 via degradation reaction similar to the reaction of von Braun type,[6] which is chlorinated to give 3. ii) When the bulky alkylamine such as N-sec-butyl- or N-tert-butylpyrrolidine[1] is used as a base, intermediate 5 can not be react with this amine and is attacked by chloride anion to give 4. Compound 4 is instantly converted to 2, which is not reacted any more with the amine under this reaction condition.

This mechanism can reasonably explain that the chlorination of 1 with phosphoryl

chloride in the presence of triethylamine give 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.[7] This mechanism is comparable with that the proposed mechanism for the reaction of phosphoryl chloride adducts of acide amides with amines to give amidines by nucleophilic attack.[8]

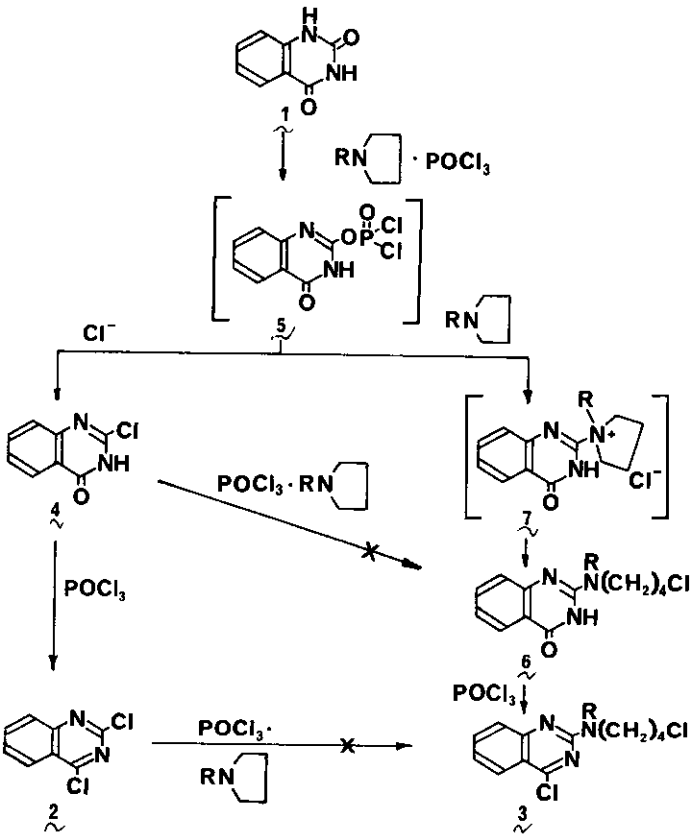

Chart 3

As the results of these studies, it has become apparent that the products ratio depends on the bulkiness rather than the basicity of the alkylamine used.

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 80-85° 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 with a similar procedure described above to give 2, mp 116-118° (90 %).

2-(4-Chloro-N-methylbutylamino)-4(3H)-quinazolone (6) —— A mixture of 1 (3.2 g), phosphoryl chloride (3.4 g) and N-methylpyrrolidine (3.5 g) in acetonitrile (300 ml) was stirred at 80-85° for 8 hr. The hot reaction mixture was filtered to recover unreacted 1 (1.8 g) and the filtrate was concentrated in vacuo to dryness. The residue was recrystallized from acetonitrile to give 1.8 g of 6 (78.3 %) as colorless needeles, mp 152°. PMR ($CDCl_3$): 1.49-2.21 (4H, m, CH_2), 3.26 (3H, s, CH_3), 3.40-3.90 (4H, m, CH_2), 7.05-8.32 (4H, m, Ar-H), 11.5 (1H, br-s, NH). IR (nujol): 3150 cm^{-1} (NH). MS m/e : 265 (M^+).

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°. The mixture was stirred for 20 min. After the excess amounts of phosphoryl chloride and N-methylpyrrolidine were evaporated off in vacuo, the residue was dissolved in 20 ml of chloroform. The chloroform solution was washed with water, satd. $NaHCO_3$ aq. and satd. NaCl aq. solution in sequence. After drying over magnesium sulfate, the chloroform layer was concentrated to give 1.4 g of 3a (87.5 %) as a pale yellow oil. The IR and PMR spectra of the product were identical with those of 4-chloro-2-(4-chloro-N-methylbutylamino)quinazoline (3a) obtained directly from 1.

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