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Fused Pyrimidines. I.[1] The Chlorination of 2,4(1*H*,3*H*)-Quinazolinedione with Phosphoryl Chloride in the Presence of *N*-Alkylcyclic Amines

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In the reaction of 2,4(1*H*, 3*H*)-quinazolinedione with phosphoryl chloride in the presence of excess *N*-methylpyrrolidine, the hydroxy groups at the 2- and 4-position of the quinazoline nucleus were replaced by the *N*-methyl-4-chlorobutylamino group and chlorine to give 4-chloro-2-(*N*-methyl-4-chlorobutylamino)quinazoline in good yield.

By using this reaction, several new 4-chloro-2-dialkylaminoquinazoline derivatives were obtained from *N*-alkylcyclic amines and 2,4(1*H*, 3*H*)-quinazolinedione.

Keywords——*N*-alkylcyclic amine; pyrrolidine; piperidine; 2,4(1*H*, 3*H*)-quinazolinedione; chlorination; amination; substitution reaction; ammonium salt; 4-chloro-2-dialkylaminoquinazoline

The chlorination of 2,4(1*H*,3*H*)-quinazolinedione (**1**) with phosphoryl chloride in the presence of triethylamine gave 4-chloro-2-diethylaminoquinazoline (**3**) as a distillable oil instead of 2,4-dichloroquinazoline (**2**). On the other hand, when tripropylamine was used as a base in place of triethylamine, compound **1** was smoothly converted to **2**.[2]

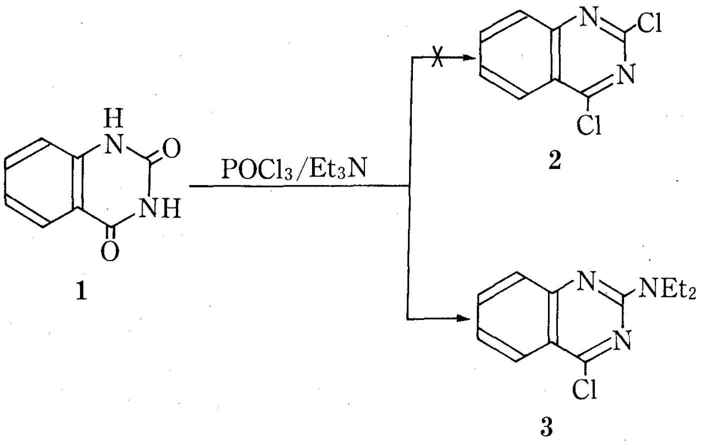


Chart 1

To extend the scope of these reactions, various *N*–alkylcyclic amines (**4**) were used in place of triethyl- or tripropylamine as a base, in an attempt to convert the hydroxy group at the 2-position in **1** to an *N*-alkyl-ω-chloroalkylamino group and to prepare 2-(*N*-alkyl-ω-chloroalkylamino)-4-chloroquinazolines (**5**) in a one-pot selective reaction.

The reaction of **1** with phosphoryl chloride in the presence of *N*-methylpyrrolidine (**4a**) was carried out at 80—85°C for 20 min to give a yellow oil (**5a**) as a major product and colorless needles as a minor product.

Compound **5a** corresponded to a molecular formula of $C_{13}H_{15}N_3Cl_2$ 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 (9:6:1) of molecular ion peaks suggested the presence of two chlorine atoms in **5a**. The proton magnetic resonance (PMR) spectrum of **5a** indicates the presence of four methylene groups(δ: 1.57—1.92, 4H and 3.37—3.89, 4H), an *N*-methyl group (δ: 3.16, 3H), and four aromatic protons (δ: 6.85—7.95, 4H). The ultraviolet (UV) spectrum of **5a** was quite similar to that of 4-chloro-2-diethylaminoquinazoline.

On the basis of these data, the structure of **5a** was established to be 4-chloro-2-(*N*-methyl-4-chlorobutylamino)quinazoline.

On the other hand, the colorless needles were identified as **2** on the basis of mp, infrared absorption (IR) and PMR spectra[3].

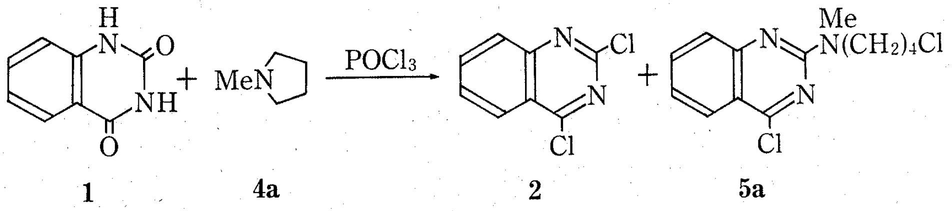


Chart 2

To clarify the relationships among **3**, **5a**, 2-chloro-4-diethylaminoquinazoline (**6**), which is an isomer of **3**, and 2-chloro-4-(*N*-methylbutylamino)quinazoline (**7**), which is an analog of **6**, the UV spectra of these compounds are shown in Fig. 1. Compound **7** was prepared by the reaction of **2** with *N*-methylbutylamine.

Compound **3** and **5a** showed a characteristic UV absorption maximum at about 380 nm, while **6** and **7** had an absorption at about 330 nm. By comparing their UV spectra in the region of about 300—400 nm, 4-chloro-2-dialkylaminoquinazolines (**3** and **5a**) and 2-chloro-4-dialkylaminoquinazolines (**6** and **7**) can be easily and unequivocally differentiated.

To investigate further the scope and limitations of this type of reaction, the study was extended to include the use of other alkylamines such as *N*-ethylpyrrolidine (**4b**), *N*-propylpyrrolidine (**4c**), *N*-butylpyrrolidine (**4b**), *N*-*sec*-butylpyrrolidine (**4e**), *N*-*tert*-butylpyrrolidine (**4f**), *N*-methylpiperidine (**4g**) and *N*-*sec*-butylpiperidine (**4h**). The results are summarized in Table I.

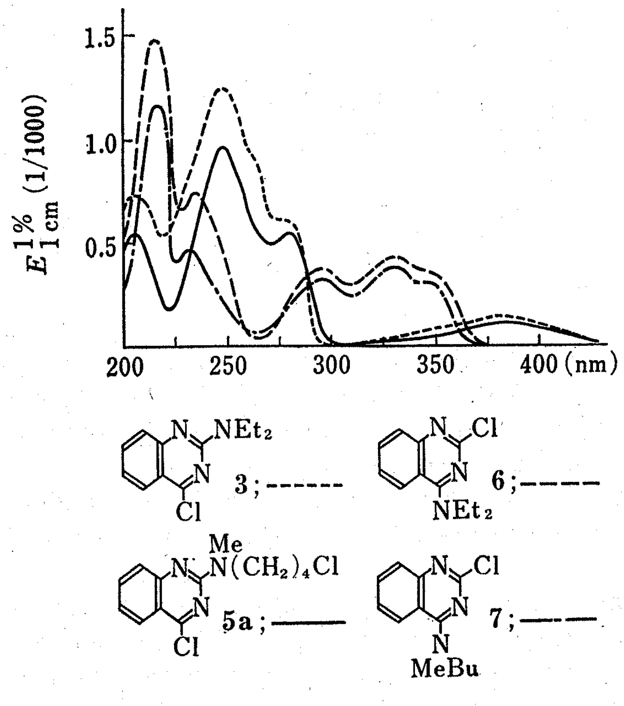


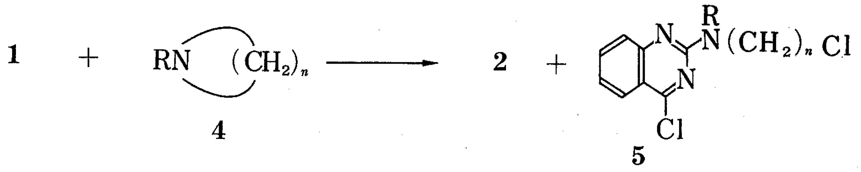
Fig. 1. UV Spectra of **3**, **5a**, **6** and **7** in EtOH

As shown in Table I, it became apparent that the reaction of **1** with phosphoryl chloride in the presence of *N*-alkylcyclic amines proceeds by a von Braun type reaction[4] through the formation of a quaternary ammonium salt which decomposes to give the new tertiary amines, 2-(*N*-alkyl-ω-chloroalkylamino)-4-chloroquinazolines (**5**).

There are two possible reaction pathways for decomposition of the quaternary ammonium salt, (a): cleavage of the *N*-alkyl group, and (b): cleavage of the cyclic amine ring. In these studies, the isolated product was mainly **5**, and 4-chloro-2-pyrrolidinoquinazoline (**8**) was not isolated.

When a bulky *N*-alkylcyclic amine such as **4e**, **4f** or **4h** was used as a base in the phosphoryl chloride chlorination of **1**, compound **2** was mainly obtained. However, when an amine such as **4a**, **4b**, **4c**, **4d** or **4g** was used, both **2** and **5** were

Table I. Yields (%) of Isolated Products from the Reaction of **1** with Phosphoryl Chloride in the Presence of **4**



4	R	*n*	**4**	R	*n*
4a	Me	4	**4e**	*sec*-Bu	4
4b	Et	4	**4f**	*tert*-Bu	4
4c	Pr	4	**4g**	Me	5
4d	Bu	4	**4h**	*sec*-Bu	5

4	**2**	**5**
4a	3.3	(**5a**)77.3
4b	17.9	(**5b**)58.7
4c	19.5	(**5c**)59.4
4d	48.5	(**5d**)34.7
4e	84.6	(**5e**)Trace
4f	88.5	(**5f**)Trace
4g	41.9	(**5g**)28.2
4h	89.4	(**5h**)Trace

obtained.

Thus, it appears that the products ratio depends on the bulkiness rather than the basicity of the alkyl amine used.

Similar reactions involving pyrimidone have been reported. King *et al.*[5] isolated 4,6-dichloro-2-methylanilinopyrimidine from the reaction mixture of barbituric acid phosphoryl chloride and dimethylaniline; 2(4)-chloro-6-methyl-4(2)-methylanilino-5-nitropyrimidine[6] was prepared from 6-methyl-5-nitrouracil in an analogous manner. Kawai *et al.*[7] heated 2,4,6-trichloropyrimidine with dimethylaniline and isolated 2,4,6-tris-methylanilinopyrimidine. Robins *et al.*[8] reported the chlorination of purinones with phosphorylchloride in the presence of aliphatic tertiary amines. In principle, these reactions appear to be of similar type.

The introduction of an *N*-alkyl-ω-chloroalkylamino group into the quinazoline nucleus by using this von Braun type reaction has not been reported in the literature.

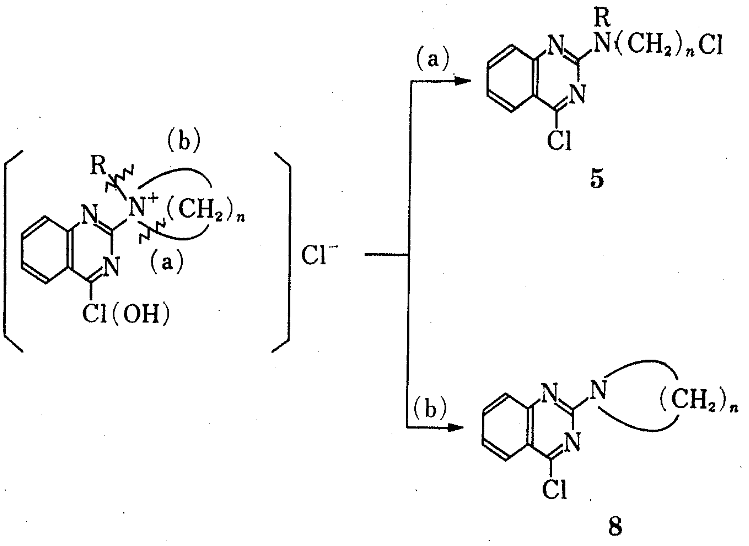


Chart 3

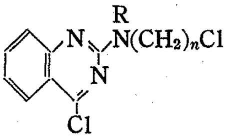
Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded by using a Hitachi EPI-G3 spectrophotometer and PMR spectra were taken with a Hitachi R-24 spectrometer; chemical shifts are 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. UV spectra were recorded with a Shimadzu UV-210 spectrophotometer. MS were measured with a Hitachi PMS-4 mass spectrometer. The refractive index was measured with an Erma refractometer. Silica gel (Kiesel gel, Merck) was used for column chromatography.

The Chlorination of 2,4(1*H*, 3*H*)-Quinazolinedione (1) with Phosphoryl Chloride in the Presence of *N*-Alkylcyclic Amines (4)——General Procedure: *N*-Alkylcyclic amine (15 ml) was added to a mixture of 1 (5.0 g, 0.031 mol) and phosphoryl chloride (70 ml), and the mixture was stirred at 80—85°C for 20 min. Excess phosphoryl chloride and 4 were evaporated off *in vacuo*, and the residue was dissolved in 100 ml of chloroform. The chloroform layer was washed with water, satd. $NaHCO_3$ aq., and then satd. NaCl aq. successively. After being dried over $MgSO_4$, the chloroform layer was concentrated to give a yellow oil. The residue was subjected to silica gel column chromatography. Elution with tetrachloromethane gave 2-(*N*-alkyl-ω-chloroalkylamino)-4-chloroquinazoline (5) as a yellow oil and 2,4-dichloroquinazoline (2) as colorless needles, mp 116—118°C.

The results are summarized in Tables II and III.

Table II. Analysis Data for **5**



Compd. No.	R	n	n_{d}^{20}	Molecular formula	Elemental analysis (%) Calcd (Found) C	H	N
5a	Me	4	1.6147	$C_{13}H_{15}N_3Cl_2$	54.94 (55.11	5.32 5.18	14.79 14.61)
5b	Et	4	1.5987	$C_{14}H_{17}N_3Cl_2$	56.38 (56.57	5.75 5.73	14.09 14.34)
5c	Pr	4	1.5960	$C_{15}H_{19}N_3Cl_2$	57.70 (57.83	6.13 6.15	13.46 13.56)
5d	Bu	4	1.5862	$C_{16}H_{21}N_3Cl_2$	58.90 (59.04	6.49 6.43	12.88 12.63)
5g	Me	5	1.6182	$C_{14}H_{17}N_3Cl_2$	56.38 (56.33	5.75 5.41	14.09 14.08)

Table III. UV, MS and PMR Spectral Data for **5**

Compd. No.	UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε)	MS *m/e* (M^+)	PMR (δ: ppm in $CDCl_3$)
5a	247(28700) 385(3300)	283, 285, 287	1.57—1.92 (4H, m, CH_2), 3.16 (3H, s, CH_3) 3.37—3.89 (4H, m, CH_2), 6.85—7.95 (4H, m, Ar-H).
5b	247(31900) 384(3200)	297, 299, 301	1.19 (3H, t, CH_3), 1.59—1.98 (4H, m, CH_2), 3.37—3.88 (6H, m, CH_2), 6.83—7.98 (4H, m, Ar-H).
5c	247(30600) 384(3100)	311, 313, 315	0.91 (3H, t, CH_3), 1.30—2.13 (6H, m, CH_2), 3.34—3.72 (6H, m, CH_2), 6.80—7.90 (4H, m, Ar-H).
5d	247(29400) 384(3100)	325, 327, 329	0.93 (3H, t, CH_3), 1.40—2.15 (8H, m, CH_2), 3.32—3.85 (6H, m, CH_2), 6.82—7.91 (4H, m, Ar-H).
5g	247(31700) 382(3100)	297, 299, 301	1.61—2.01 (6H, m, CH_2), 3.19 (3H, s, CH_3), 3.39—3.96 (4H, m, CH_2), 6.85—8.05 (4H, m, Ar-H).

2-Chloro-4-(*N*-methylbutylamino)quinazoline (7)——*N*-Methylbutylamine (1.9 g, 0.022 mol) in 15 ml of dichloromethane was added to a solution of 2 (2.0 g, 0.010 mol) in 50 ml of dichloromethane at 20—30°C, and the mixture was stirred at 20—30°C for 20 min. The resulting mixture was poured into ice-water. The dichloromethane layer was separated and washed with water. After being dried over $MgSO_4$, the extract was concentrated to give colorless crystals which were recrystallized from *n*-hexane to give 2.1 g (84.2%) of **7** as colorless needles, mp 59°C. *Anal.* Calcd for $C_{13}H_{16}N_3Cl$: C, 62.52; H, 6.46: N, 16.83. Found: C, 62.84; H, 6.54; N, 16.90. PMR ($CDCl_3$): 0.97 (3H, t, CH_3), 0.65—2.05 (6H, m, CH_2), 3.35 (3H, s, CH_3), 3.71 (2H, t, CH_2), 7.15—8.01 (4H, m, Ar-H). UV (λ_{max}^{EtOH}): nm (ε); 232 (12000), 296 (7900), 329 (9100), 342 (7300).

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References and Notes

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