HETEROCYCLES, Vol. 19, No. 10, 1982

THE REACTION OF 2,4-DICHLOROQUINAZOLINE WITH N-ALKYLPYRROLIDINES

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Abstract—— The reaction of 2,4-dichloroquinazoline with N-methylpyrrolidine gave N-(2-chloro-4-quinazolinyl)-N-methylpyrrolidinium chloride, which was heated to give 2-chloro-4-(N-methyl-4-chlorobutylamino)quinazoline and reacted also with water in the presence of excess N-methylpyrrolidine to give a stable zwitter ion, 4-(N-methylpyrrolidino)-2-quinazolinolate.

In the preceding papers,[1-3] one of the authors has reported that the reaction of 2,4-(1H, 3H)-quinazolinedione (1) with N-alkylaminopyrrolidines (2) in phosphoryl chloride undergoes readily a von Braun type reaction through the formation of 4-oxo-3,4-dihydro-2-quinazolinyl dichlorophosphate and N-(4-oxo-3,4-dihydro-2-quinazolinyl)-N-alkylpyrrolidinium chloride in sequence, which decomposes to give 2-(N-alkyl-4-chlorobutylamino)-4-chloroquinazoline (3).

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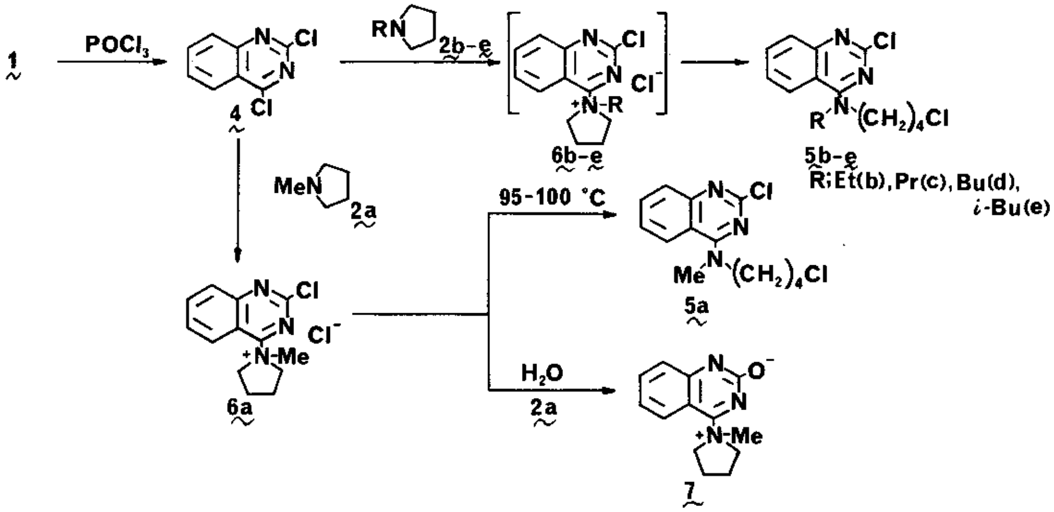
To extend the scope of these reactions, compound 2 was used as a nucleophile, in an attempt to convert the chlorine at the 4-position in 2,4-dichloroquinazoline (4) to an N-alkyl-4-chlorobutylamino group and to prepare 4-(N-alkyl-4-chlorobutylamino)-2-chloroquinazoline (5), which was an isomer of 3.

In the hope of obtaining 5, 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-methyl-4-chlorobutylamino)quinazoline (5a), but N-(2-chloro-4-quinazolinyl)-N-methylpyrrolidinium chloride (6), mp 88-90°(dec.). When compound 6 was stirred at 95-100° for 1 h, compound 5a was obtained. On the other hand, the reaction of 6 with water in the presence of excess 2a gave a stable zwitter ion, 4-(N-methylpyrrolidino)-2-quinazolinolate (7).

The structure 5a was confirmed on the basis of UV, ^1H-NMR, mass spectra and elemental analysis data. These data are given in experimental section.

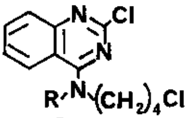
The molecular formula of 7 was determined to be $C_{13}H_{15}N_3O$ on the basis of its elemental analysis data and MS (M^+, m/e: 229). Compound 7 showed a characteristic ^1H-NMR spectrum (in $CDCl_3$), which indicated the presence of an N-methylpyrrolidinium moiety (δ: 1.95-2.36, 4H, m; 3.26-3.67, 2H, m; 3.45, 3H, s; 4.69-5.06, 2H, m). On the other hand, the ^1H-NMR spectrum observed in D_2O (δ: 1.60-2.35, 4H, m; 3.15-3.76, 2H, m; 3.25, 3H, s; 3.90-4.35, 2H, m for N-methylpyrrolidinium moiety) was markedly different from that observed in $CDCl_3$. This fact suggests that compound 7 is hydrated with D_2O. The IR spectrum of 7 indicated that it has no hydroxyl and carbonyl groups. On the basis of these data, the structure 7 was considered to be a zwitter ion, 4-(N-methylpyrrolidino)-2-quinazolinolate, which was also supported by the ^{13}C-NMR spectrum as shown in the experimental section.



Then, compound 4 was allowed to react with N-ethylpyrrolidine (2b) under a similar reaction conditions as described for 6. However, intermediary quaternary ammonium chloride was not isolated and 2-chloro-4-(N-ethyl-4-chlorobutylamino)quinazoline (5b) was obtained directly.

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-iso-butyl- (2e), N-sec-butyl- (2f) and N-tert-butylpyrrolidine (2g). The results are summarized in Table I.

Table I. Yields (%) of Isolated Products from the Reaction of 2 with 4



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

*) Yield from 6.

From these results, it becomes apparent that the reaction of 4 with 2a produces stable quaternary ammonium chloride (6), and 6 decomposes to give 5a and reacts also with water in the presence of a base to give a stable zwitter ion. However, a bulky amine, such as 2b, 2c, 2d or 2e, is allowed to react with 4, the quaternary ammonium salt formed decomposes immediately to give 4-(N-alkyl-4-chlorobutylamino)-2-chloroquinazolines (5) in good yields. An even bulkier amine, such as 2f or 2g, can not react with 4 any more.

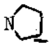
EXPERIMENTAL

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. After the excess of 2 and acetone were evaporated off in vacuo, the residue was dissolved in chloroform (50 ml). The extract was washed with water and then dried over magnesium sulfate. The chloroform layer was concentrated to give a pale yellow oil, which was subjected to silica gel column chromatography. Elution with toluene gave 4-(N-alkyl-4-chlorobutylamino)-2-chloroquinazoline (5). The results are summarized in Table II.

2-Chloro-4-(N-methyl-4-chlorobutylamino)quinazoline (5a) —— Compound 6 (1.00 g) was stirred at 95-100°C for 1 h to give 0.67 g (67.0 %) of 5a as colorless needles, mp 67-69°C. The ^{1}H-NMR and mass spectral data are listed in Table II.

Table II. 4-(N-Alkyl-4-chlorobutylamino)-2-chloroquinazolines

Compound No.	mp (°C)	MS (M^+) m/e	^{1}H-NMR (δ: ppm in $CDCl_3$)
5a	67-69	283, 285, 287	1.50-2.31(4H,m,CH_2x2),3.31-4.10(4H,m,CH_2x2),3.38(3H,s,CH_3),7.05-8.20(4H,m,Ar-H).
5b	62-65	297, 299, 301	1.36(3H,t,CH_3),1.30-2.42(4H,m,CH_2x2),2.92-4.00(6H,m,CH_2x3),6.92-8.01(4H,m,Ar-H).
5c	61-62	311, 313, 315	0.98(3H,t,CH_3),1.37-2.30(6H,m,CH_2x3),3.15-4.21(6H,m,CH_2x3),7.04-7.85(4H,m,Ar-H).
5d	38-40	325, 327, 329	0.95(3H,m,CH_3),1.11-2.51(8H,m,CH_2x4),3.12-4.21(6H,m,CH_2x3),6.94-8.02(4H,m,Ar-H).
5e	48-50	325, 327, 329	0.88(6H,d,CH_3x2),1.29-2.45(5H,m,CH_2x2 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,Ar-H).

4-(N-Methylpyrrolidino)-2-quinazolinolate (7) —— 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 7 as colorless needles, mp 182°C. ^{1}H-NMR ($CDCl_3$): 1.95-2.36 (4H, m, CH_2 x 2), 3.26-3.67 (2H, m, CH x 2), 3.45(3H, s, CH_3), 4.69-5.06 (2H, m, CH x 2), 7.23-7.70 (3H, m, Ar-H), 8.20-8.38 (1H, br d, Ar-H). ^{1}H-NMR (D_2O): 1.60-2.35 (4H, m, CH_2 x 2), 3.15-3.76 (2H, m, CH x 2), 3.25 (3H, s, CH_3), 3.90-4.35 (2H, m, CH x 2), 7.00-7.40 (3H, m, Ar-H), 7.71-7.90 (1H, br d, Ar-H). ^{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), 121.2 (s, C-4a), 149.2 (s, C-8a), 50.8 (q, N-CH_3), 62.1 (t, ), 21.4 (t, ).

ACKNOWLEDGEMENT The authors are grateful to Mr. K. Tanabe, director of Research Laboratories, Agricultural Chemicals Division, for his permission to publish this paper and to Drs. K. Konishi, H. Nagase, T. Kamikado and E. Mizuta for their encouragement throughout this work.

REFERENCES AND NOTES

1) H. Miki, Heterocycles, 19, 7 (1982). 2) H. Miki, Chem. Pharm. Bull., "in press". 3) H. Miki, Heterocycles, 19, 15 (1982). 4) I. Ya. Postovskii and I. N. Goncharova, Zh. Obshch. Khim., 32, 3323 (1962); C. A., 58, 12555a (1963). 5) The structures of all new compounds were confirmed on their ^{1}H-NMR, ^{13}C-NMR, IR, UV and mass spectra in addition to the elemental analyses for C, H and N.

Received, 8th March, 1982