SYNTHESIS OF 2,4-DIAMINOQUINAZOLINE DERIVATIVES

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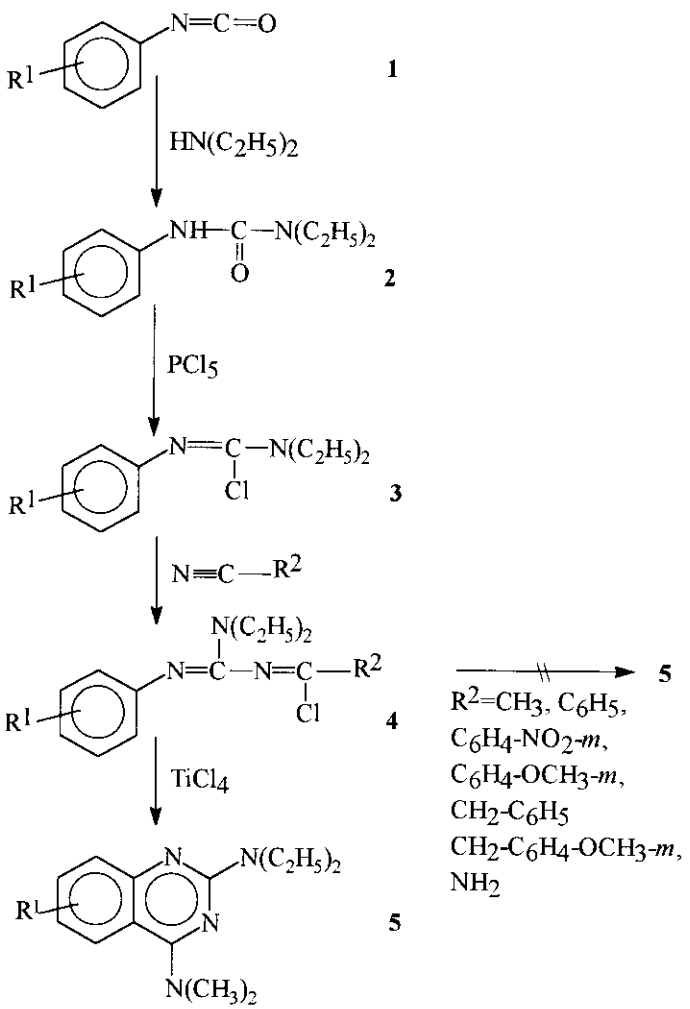
Abstract- A series of 6- and 7-substituted derivatives of 2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline have been synthesized. The synthesis consists in converting *N*-phenyl-*N',N'*-diethylurea into chloroamidines which are treated with *N,N*-dimethylcyanamide to 1-chloro-2,4-diaza-1,3-butadiene derivatives, followed by a cyclization to quinazoline derivatives.

Quinazolines have been attracting attention for a few decades due to a wide range of biological activity.[1] Particular attention has been focused on 2-amino, 4-amino and 2,4-diamino derivatives which demonstrate anti-malaria and cancerogenic properties, and are used to work out medicines against hypertension and to fight infections involving AIDS.[2] 2,4-Diaminoquinazolines can be also potentially used as DHFR inhibitors.[3] The most popular method to obtain 2,4-diaminoquinazoline derivatives is the nucleophilic displacement of appropriate chloro derivatives of quinazoline with amines.[4] The other of the described methods involves the reaction of *o*-aminobenzonitriles with dicyanodiamide or cyanamide.[4] We wish to report now a new method for the synthesis of 2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline

derivatives (**5**, R^2=$N(CH_3)_2$) which consists in converting urea derivatives (**2**) into chloroamidine derivatives (**3**) followed by their reaction with nitriles ($N(CH_3)_2$ etc.) and cyclization of the formed linear product (**4**, R^2=$N(CH_3)_2$), as shown in Scheme 1.

Scheme 1. Synthesis of 2-(*N,N*-diethylamino)-4-R^2-substituted quinazoline derivatives



R^2=$N(CH_3)_2$

R^1=H, Cl, OCH_3, NO_2.

Phenyl isocyanate derivatives substituted with an electron-donating or -withdrawing group at the 3 or 4 positions (**1**) were used as starting materials. They were converted into *N*-phenyl-*N'*,*N'*-diethylurea derivatives (**2**) (Table 1) by the reaction with *N,N*-diethylamine.[5]

Table 1. Characteristics of *N*-phenyl-*N'*,*N'*-diethylurea derivatives (**2**)

Product	R	Yield [%]	mp [°C]	mp [°C]	R_f[a)]
2a	H	86.0	84-86 (ethanol)	85[b)]	0.47
2b	3-Cl	71.5	88-89 (ethanol)	89-90[c)]	0.43
2c	4-Cl	69.0	116-117 (ethanol)	116-118[c)]	0.42
2d	3-OCH_3	79.2	56-58 (ethanol)	---	0.37
2e	4-OCH_3	87.9	59-60 (acetone)	61.5-62[c)]	0.44
2f	3-NO_2	69.5	85-87 (acetone)	88-89[c)]	0.44
2g	4-NO_2	87.5	161-162 (acetone)	162[d)]	0.36

a) TLC; silica gel; 6:2:1[v/v/v] benzene:ethyl acetate:diethylamine

b) ref. [5]

c) ref. [6]

d) ref. [7]

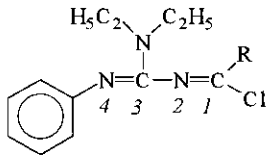
Substituted ureas (**2**) reacted then quite easily with phosphorus pentachloride, yielding *N*^{1},*N*^{1}-diethyl-*N*^{2}-phenylchlorocarboxyamidines (**3**). These products reacted with *N*,*N*-dimethylcyanamide to give the acyclic intermediate products (**4**, R^2=$N(CH_3)_2$), the derivative of 1-chloro-2,4-diaza-1,3-butadiene,[8] which further underwent cyclization under relevant conditions. Apart from *N*,*N*-dimethylcyanamide, some other nitriles were also subjected to the *N*-imidoylation reaction: acetonitrile, benzonitrile, *m*-nitrobenzonitrile, *m*-methoxybenzonitrile, phenylacetonitrile, *m*-methoxyphenylacetonitrile and cyanamide. Unfortunately, none of them led to quinazoline derivatives, although *N*-imidoylation reactions occurred.

To solve this problem we made the MNDO calculations of effective atomic charge for the intermediate products and cations generated from them, for three selected compounds (**4**, R^2=CH_3, NH_2, $N(CH_3)_2$) (Table 2). The distributions of free-electron density in the linear intermediate products (**4.1, 4.2, 4.3**) are comparable. The most polarized C-1~1-Cl bond prove to be the one of *N*,*N*-dimethylamine substituted compound (**4.3**). Effective atomic charges for respective cations proved that the charge at C-1 atom for the cation (**4.1**, R=CH_3) is too small to promote the cyclization process. The values of charges at the carbon

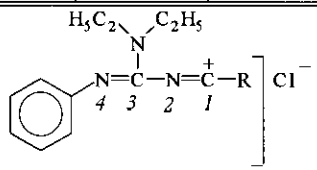
C-1 atom for cations (**4.2**, R=NH_2) and (**4.3**, R=$N(CH_3)_2$), are much higher than the respective value for the cation (**4.1**, R=CH_3), and are apparently favourable for the cyclization process.

In fact, the products of *N*-imidoylation reaction of *N,N*-dimethylcyanamide (**4**, R^2=$N(CH_3)_2$) underwent cyclization when heated over a few hours in a solvent at raised temperature in the presence of $TiCl_4$.

Table 2. MNDO calculations for 1-chloro-3-amino-4-phenyl-2,4-diaza-1,3-butadiene intermediates and cations derived them.



Product	R	Effective charge				
		N-4	C-3	N-2	C-1	1-Cl
4.1	CH_3	-0.2776	0.3242	-0.2767	0.2037	-0.1277
4.2	NH_2	-0.2718	0.3301	-0.3397	0.3156	-0.1125
4.3	$N(CH_3)_2$	-0.2746	0.3400	-0.3219	0.3662	-0.1354



Product	R	Effective charge			
		N-4	C-3	N-2	C-1
4.1	CH_3	-0.2820	0.4350	-0.1940	0.0520
4.2	NH_2	-0.2025	0.3673	-0.1421	0.3750
4.3	$N(CH_3)_2$	-0.2280	0.3820	-0.1540	0.3910

The stable quinazoline-catalyst complexes thus formed were broken using the concentrated hydrochloric acid solution. In this way we obtained seven derivatives of 2-(*N,N*-diethylamino)-4-(*N,N*-dimethyl-amino)quinazoline (**5**), substituted at the 6 or 7 position with an electron-donating and -withdrawing groups (R_1=H, Cl, OCH_3, NO_2). The structure of the obtained compounds is confirmed by the elementary analysis and ^{1}H-NMR and MS spectroscopies (Table 3, Table 4).

Table 3. Characteristics of (6,7)-R-2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazolines

Product	R	Molecular formula	Found			Calculated			MS (70 ev)
			C	H	N	C	H	N	m/z[int. %]
5a	H	$C_{14}H_{20}N_4 \times H_2O \times HCl$	55.52	7.79	18.38	56.26	7.70	18.74	244 (38.8)
5b	7-Cl	$C_{14}H_{19}N_4 \times H_2O \times HCl$	49.71	6.78	16.55	50.45	6.66	16.80	278 (36.9)
5c	6-Cl	$C_{14}H_{19}N_4 \times H_2O \times HCl$	50.19	6.62	16.70	50.45	6.66	16.80	278 (35.4)
5d	7-OCH_3	$C_{15}H_{22}N_4O \times H_2O \times HCl$	51.51	7.50	16.01	54.78	7.68	17.03	274 (29.4)
5e	6-OCH_3	$C_{15}H_{22}N_4O \times H_2O \times HCl$	54.40	7.70	16.98	54.78	7.68	17.03	274 (41.5)
5f	7-NO_2	$C_{14}H_{19}N_5O_2$	58.18	6.88	24.22	58.10	6.63	24.21	289 (42.1)
5g	6-NO_2	$C_{14}H_{19}N_5O_2$	57.16	6.70	23.88	58.10	6.63	24.21	289 (34.5)

The yields of the obtained products fairly varied, but the influence of particular substituent type on the yield has not been noticed. It was particularly difficult to break the stable quinazoline-catalyst complexes and to obtain pure quinazolines from the post-reaction mixtures, which, according to our opinion, influences the reaction yield. 2-(*N,N*-Diethylamino)-4-(*N,N*-dimethylamino)quinazolines, which are characteristic of the presence of four basic centers, two exocyclic nitrogen atoms of the di-substituted amine groups and two endocyclic nitrogen atoms of the quinazoline ring, could operate as the hydrogen trap. The results of the elementary analysis confirmed that they bind hydrogen chloride very strongly. Only two nitro derivatives (**5g, 5f**) could be separated definitely in free forms (Table 3); the other quinazolines (**5a-5e**) were separated as hydrochloride hydrates (R^1=H, Cl, OCH_3). The compounds (**5a-5e**) are resistant to deprotonation and do not convert into free quinazolines, even when treated with the 20% (6.15 M) solution of NaOH at room temperature.

The X-Ray structural analysis of 7-methoxy-2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline hydrochloride shows that as in the case of 4-(*N,N*-dimethylamino)-2-phenylquinazoline derivatives[9] the protonation centre is the nitrogen atom at position 1.

Table 4. Characteristics of (6,7)-R-2-(*N*,*N*-diethylamino)-4-(*N*,*N*-dimethylamino)quinazolines

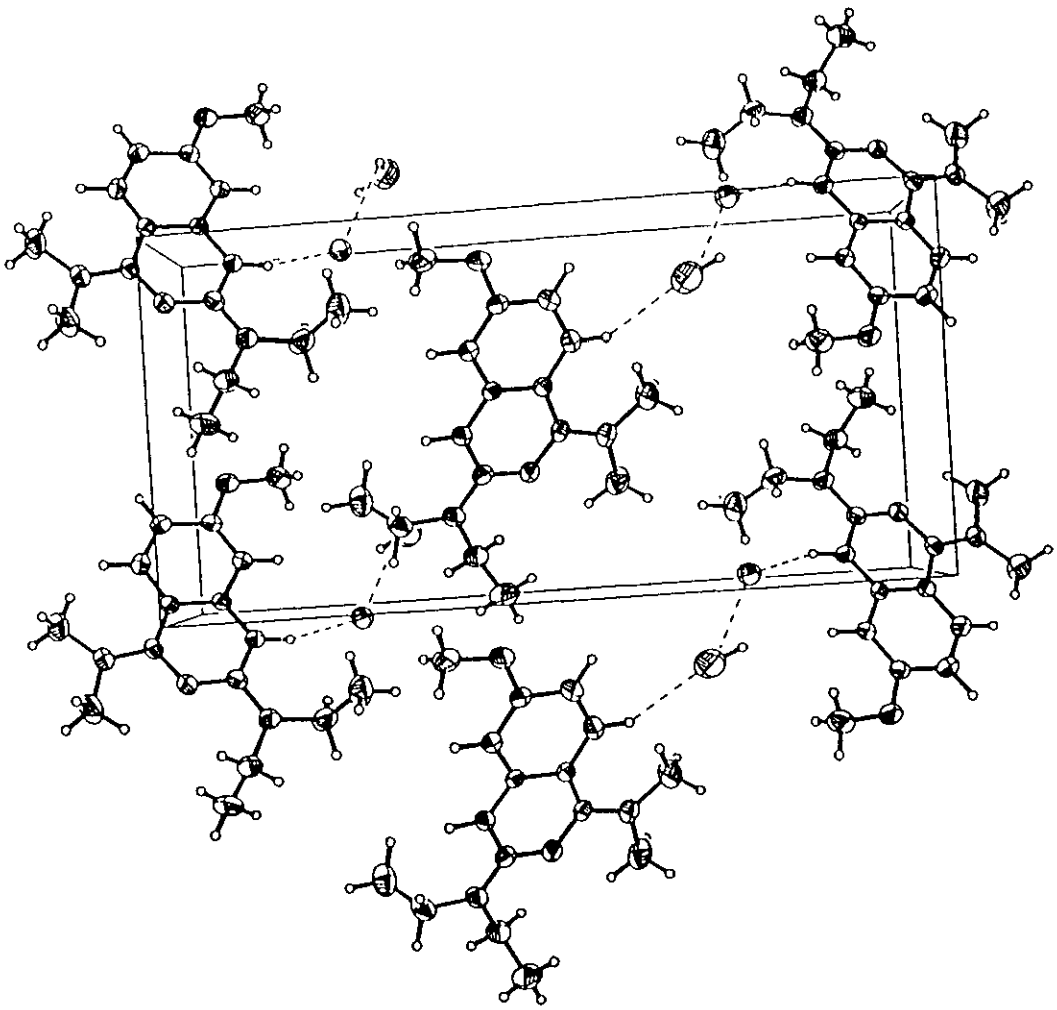
Product	R	Yield[a] [%]	mp [°C]	R_f[b]	^{1}H-NMR ($CDCl_3$-TMS) δ [ppm]
5a	H	78.8	125-127 (benzene)	0.64	1.29 [t, 6H, J=7.30 Hz, N(CH_2**CH_3**)$_2$], 3.48 [s, 6H, N(CH_3)$_2$], 3.77 [q, 4H, J=7.30 Hz, N(**CH_2**CH_3)$_2$], 7.25 [dd, 1H, J=7.80, 8.40 Hz, H-6], 7.64 [dd, 1H, J=7.80, 8.40 Hz, H-7], 7.87 [d, 1H, J=8.40 Hz, H-5], 8.13 [d, 1H, J=8.40 Hz, H-8]
5b	7-Cl	69.5	222-223 (methanol)	0.63	1.30 [t, 6H, N(CH_2**CH_3**)$_2$], 3.50 [s, 6H, N(CH_3)$_2$], 3.70 [q, 4H, N(**CH_2**CH_3)$_2$], 7.00-8.30 [m, 3H]
5c	6-Cl	58.2	202-204 (methanol)	0.67	1.30 [t, 6H, N(CH_2**CH_3**)$_2$], 3.50 [s, 6H, N(CH_3)$_2$], 3.70 [q, 4H, N(**CH_2**CH_3)$_2$], 7.30-8.20 [m, 3H]
5d	7-OCH_3	42.0	135-137 (acetone)	0.74	1.28 [t, 6H, N(CH_2**CH_3**)$_2$], 3.44 [s, 6H, N(CH_3)$_2$], 3.70 [q, 4H, N(**CH_2**CH_3)$_2$], 3.96 [s, 3H, OCH_3], 6.80 [d, 1H, H-6], 7.79 [d, 1H, H-5], 8.60 [s, 1H, H-8]
5e	6-OCH_3	47.7	139-140 (acetone)	0.65	1.28 [t, 6H, N(CH_2**CH_3**)$_2$], 3.48 [s, 6H, N(CH_3)$_2$], 3.60-4.15 [m, 7H, N(**CH_2**CH_3)$_2$, OCH_3], 8.87 [d, 1H, H-6], 7.30 [m, 2H, H-7, H-5]
5f	7-NO_2	78.6	85-87 (hexane)	0.62	1.21 [t, 6H, N(CH_2**CH_3**)$_2$], 3.25 [s, 6H, N(CH_3)$_2$], 3.66 [q, 4H, N(**CH_2**CH_3)$_2$], 7.46 [d, 1H, H-6], 7.84 [d, 1H, H-5], 8.25 [s, 1H, H-8]
5g	6-NO_2	36.6	95-98 (hexane)	0.65	1.26 [t, 6H, N(CH_2**CH_3**)$_2$], 3.36 [s, 6H, N(CH_3)$_2$], 3.71 [q, 4H, N(**CH_2**CH_3)$_2$], 7.36 [d, 1H, H-7], 8.20 [d, 1H, H-8], 8.80 [s, 1H, H-5]

a) Yield in respect to original urea

b) TLC; silica gel; 6:2:1[v/v/v] benzene:ethyl acetate:diethylamine

However, unlike the 2-(4'-methoxyphenyl)-4-(*N,N*-dimethylamino)quinazoline hydrochloride, where the elementary cell is composed of two quinazoline molecules, two ionic HCl units and one water molecule (N1---H---Cl---H---O---H---Cl---H---N1) joined regularly, in the case of 7-methoxy-2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline hydrochloride, each organic molecule binds with one HCl unit and one water molecule (N1---H---Cl---H---**O**---H). However oxygen atom of the water molecule does not interact with the nitrogen atom N1 through the chlorine atom Cl, and indirectly with hydrogen atoms, but it does mainly with the carbon C-5 atom through the hydrogen atom $H_{C\text{-}5}$ (Scheme 2).

Scheme 2. Single crystal X-Ray diffraction analysis of 7-methoxy-2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline hydrochloride



Furthermore, the X-Ray structural analysis of the investigated hydrochloride confirms the results of elementary analysis for five quinazolines (**5a-5e**) obtained as the hydrated hydrochlorides.

EXPERIMENTAL

Synthesis of *N*-(R^1-phenyl)-*N'*,*N'*-diethylurea (2)

The appropriate R^1-phenyl isocyanate (0.10 mol) in 100 mL of anhydrous benzene was placed in a 250 mL two necked flask equipped with a stirrer and a dropping funnel. A solution of *N,N*-diethylamine (0.11 mol, 7.9 g, 11.2 ml) in 50 mL of benzene was added dropwise under agitation and cooled. After the dropping of amine was completed, the agitation was continued for about 30 min. Excess of benzene and *N,N*-diethylamine were removed using a rotary evaporator. Then a crude urea derivative was recrystallized (acetone, ethanol).

Synthesis of 2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline derivative (5)

The appropriate *N*-(R^1-phenyl)-*N'*,*N'*-diethylurea (**2**) (0.05 mol), 150 mL of anhydrous benzene and PCl_5 (11.5 g, 0.055 mol) were placed in a 250 mL three necked flask equipped with a stirrer and an air condenser to which calcium chloride-containing drying tube was afixed. The mixture was gently heated at about 50°C until the disappearance of urea (TLC) was completed. Benzene and $POCl_3$ were removed using a rotary evaporator. Anhydrous benzene (100 mL) and *N,N*-dimethylcyanamide (3.5 g, 0.05 mol) were added to the crude *N*-phenylbenzimidoyl chloride (**3**). The mixture was left for 24 h and then, $TiCl_4$ (5 mL, 0.05 mol) in 20 mL of anhydrous benzene was added dropwise followed by agitation at 50°C for 3 h. Benzene was decanted from the resulting gluey solid and 200 mL of 20% aqueous HCl was added. The mixture was left to hydrolyze and then filtered under vacuum. The obtained solids were rinsed. The solution was neutralized with 20% aqueous NaOH, yielding a precipitate which was extracted few times with chloroform. The combined extracts were dried over $MgSO_4$ and concentrated yielding an oily residue

which was purified using an adsorption at decolorizing charcoal in methanol. After filtration, the methanol was removed using a rotary evaporator and the dry residue was crystallized (acetone,benzene, hexane, methanol). In the case of difficulties in crystallization a preparative chromatography was done (silica gel for TLC; 6:2:1[v/v/v] benzene:ethyl acetate:diethylamine).

Data from single crystal X-Ray analysis of 7-methoxy-2-(*N*,*N*-diethylamino)-4-(*N*,*N*-dimethylamino)-quinazoline hydrochloride (5d): $C_{15}H_{22}N_4O \times HCl \times H_2O$; MW 328.80, monoclinic crystal system, $P2_1/n$, a=8.927(3), b=9.844(2), c=19.902(4)Å, β=95.10(2)°, Vol=1741.5 (8)Å^3, D_{calc}=1.254 mg/m^3, $\mu(MoK_\alpha)$=0.232 mm^{-1}, MoK_α, λ=0.71073Å.

Analysis of products

^{1}H-NMR spectra were recorded at 25°C by BRUKER AM 500 (**5a**), TESLA BS 587 (80 MHz) (**5b, 5c**) and VARIAN INOVA 300 (**5d-5g**) spectrometers. MS spectra were made by SHIMADZU QP-200 mass spectrometer. Single crystal X-Ray analysis was made by SIEMENS R3m/V apparatus. Elementary analysis was carried out by means of PERKIN-ELMER 240 c analyzer.

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