A Study Concerning the Synthesis, Basicity and Hydrolysis of 4-Amino-2-(*N*,*N*-diethylamino)quinazoline Derivatives

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A group of 2-(*N*,*N*-diethylamino)-4-aminoquinazoline derivatives have been synthesized in the reaction of N^1,N^1-diethyl-N^2-arylchlorocarboxyamidines with cyanamide in the presence of $TiCl_4$ as a catalyst. Such quinazolines decompose into the corresponding quinazolones in dilute aqueous HCl solutions at higher temperature. Hydrolysis rates of 2-(*N*,*N*-diethylamino)-4-aminoquinazoline and 2-(*N*,*N*-diethylamino)-4-(*N*,*N*-dimethylamino)-quinazoline have been determined to observe the influence of substituents at the 4-amino group upon the hydrolysis. pK_a values have been also determined for these compounds and analyzed in conjunction with the Hammett σ constants.

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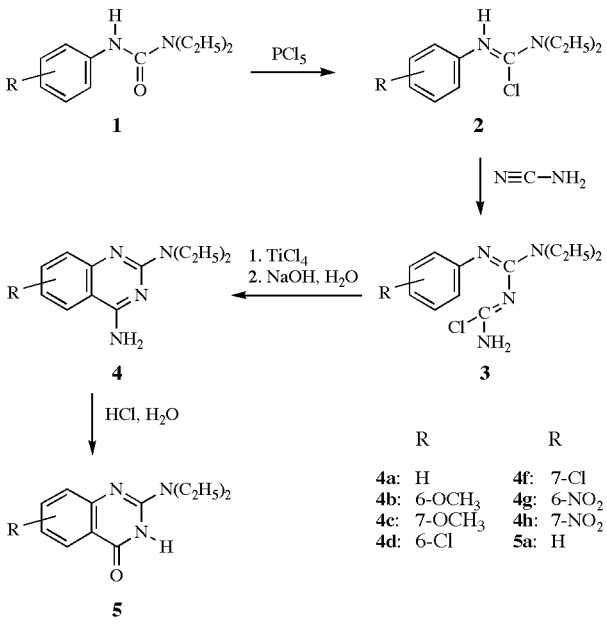
The work described here forms a part of our general program on the synthesis of the 4-aminoquinazolines due to their pharmacologic activity. Some of these compounds were found to be inhibitors of the tyrosine kinase [1,2] or dihydrofolate reductase enzymes [3,4] so they work as potent anticancer agents. The methods making use of *N*-phenylbenzimidoyl chlorides or esters in the synthesis of the arrangement of that type were initiated by Meerwein and co-workers [5]. There are some references that 2-amino- and 2,4-diaminoquinazolines could be obtained starting from chlorocarboxyamidine derivatives [6,7]. First attempts involving the application of cyanamide in the cyclization of chlorocarboxyamidines in the presence of $TiCl_4$ as a catalyst gave negative results [7]. We have renewed our attempts encouraged by MNDO calculations not excepting such reaction possibility. In the present paper, we are reporting on the synthesis of 2-(*N*,*N*-diethylamino)-4-aminoquinazoline derivatives substituted in the position 6 or 7 with electron-donating and withdrawing groups, the basicity and some kinetic aspects of the hydrolysis of 2,4-diaminoquinazolines.

N^1,N^1-Diethyl-N^2-arylchlorocarboxyamidine derivatives (**2**) were obtained in the reaction of the previously described [7] *N*-aryl-*N'*,*N'*-diethylureas (**1**) with $SOCl_2$, $POCl_3$ or PCl_5, but the best results were afforded with the use of the last agent. The crude N^1,N^1-diethyl-N^2-arylchlorocarboxyamidines, which were obtained in near quantitative yields, are usually yellowish oils having unpleasant irritating odours. Similarly to the typical imidoyl chlorides [8], they are highly reactive substances and must often be prepared as required, because they are very sensitive to moisture, forming the starting ureas. N^1,N^1-Diethyl-N^2-arylchlorocarboxyamidine derivatives (**2**, Scheme 1) react with cyanamide at room temperature to give a linear product, a derivative of 4-amino-1-aryl-4-chloro-2-(*N*,*N*-diethylamino)-2,4-diaza-1,3-butadiene (**3**). Such compounds cyclize at the next step to corresponding 2-(*N*,*N*-diethylamino)-4-aminoquinazolines (**4**) at higher temperature in an anhydrous inert solvent in the presence of $TiCl_4$ as catalyst.

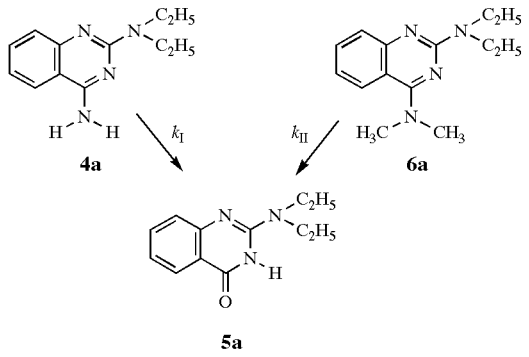
Scheme 1



A great advantage of titanium tetrachloride in comparison to other often used Lewis acid catalysts is the stabilisation of the *cis* arrangement of the diene complex (**3**) of the cyclizing linear product. Highly stable quinazoline-catalyst complexes were broken with the use of concentrated inorganic base solutions and the crude quinazolines were immediately removed from the reaction medium *via* extraction. According to the presented scheme, a new group of 2-(*N*,*N*-diethylamino)-4-aminoquinazoline (**4a-4g**) and 3,4-dihydro-2-(*N*,*N*-diethylamino)-4-quinazolone (**5a**) have been synthesized. The reaction yields, with respect to the initial ureas varied slightly, and are the lowest as expected for quinazolines with electron-withdrawing groups (**4f**, **4g**).

The difficulties with the separation of the quinazolines from post-reaction mixtures and the consecutive hydrolysis of 4-aminoquinazolines (**4**) to the corresponding 3,4-dihydro-4-quinazolones (**5**) adversely affect the product yield. It was particularly interesting at this stage to determine the hydrolysis rates of 2-(*N*,*N*-diethylamino)-4-aminoquinazoline (**4a**) and 2-(*N*,*N*-diethylamino)-4-(*N*,*N*-dimethylamino)-quinazoline (**6a**) because there are some contradictory references on the hydrolysis of several 4-aminoquinazolines [9,10,11]. The kinetic study shows that quinazoline (**4a**) converts to the corresponding quinazolone (**5a**) in the dilute aqueous HCl solution at the temperature of 80 °C about 10 times faster (Scheme 2, k_I=6.12(±0.84)*10^{-5} s^{-1}) than the substituted compound (**6a**) (k_{II} =6.52(±0.34)*10^{-6} s^{-1}). It should be mentioned that 2,4-diaminoquinazolines have two potential sites of hydrolysis [12,13] and it was particularly interesting to determine which site is more susceptible to hydrolysis. The quinazoline **6a**, while heating in a boiling 5% aqueous HCl solution for a few days, afforded only one product - 3,4-dihydro-2-(*N*,*N*-diethylamino)-4-quinazolone (**5a**). The *N*,*N*-diethylamino group at the position 2 of such the quinazolone remained unconverted.

Scheme 2



The determination of the dissociation constants pK_a of 4-amino-2-(*N*,*N*-diethylamino)quinazolines (**4a-4g**) was performed according to the spectrophotometric method of Albert and Serjeant [14] in 50% aqueous methanol solution (10^{-5} *M*, room temperature). The results show that the donosicity of the substituent in the 6 or 7 position of the quinazoline ring in 4-amino-2-(*N*,*N*-diethylamino)quinazolines greatly affects pK_a values. Donor substituents cause an increase in basicity (higher pK_a values) compared with pK_a of the original arrangement (R=H) and withdrawing substituents cause a decrease (lower pK_a values). The determined dissociation constants pK_a correlated well with appropriate Hammett σ_m constants [15] for 6-R substituted compounds and σ_p constants for 7-R substituted compounds (Equation: pK_a: -2.335*σ + 7.794; the Number of data points used: *N*: 7; Residual sum of squares: *S*: 0.170; Coefficient of determination: *r*: 0.985). This correlation is consistent with Charton's results on 6- and 7-substituted quinolines [16], investigations on electron interactions in monosubstituted alternating systems [17] and our earlier research on the basicity of 4-amino-2-phenylquinazolines [18]. It should be mentioned here that a different correlation was applied in the case of 4-(*N*,*N*-dimethylamino)-quinazoline derivatives [19]. The bulky group in this position causes a decrease of the electron density of the C-4-C-4a bond and that is why the electron transfer occurs in such systems in the way as in the substituted aniline. Generally, 4-amino-2-(*N*,*N*-diethylamino)quinazolines (**4a-g**) (pK_a values of the examined series: 5.99 – 8.31) are stronger bases than the corresponding 4-amino-2-phenylquinazolines (pK_a values of the examined series: 5.33 - 6.40) [18]. Such a difference in basicity is caused by electronic effects of the substituent in the position 2, that is closest to the protonated ring nitrogen atoms.

EXPERIMENTAL

UV spectra were recorded by Shimadzu UV-2102 spectrophotometer; basic medium: 0.05 *M* NaOH in 50% aqueous methanol solution, acidic medium: 0.05 *M* HCl in 50% aqueous methanol solution. Elemental analyses were carried out by means of Perkin Elmer 240c analyser. ^{1}H and ^{13}C nmr spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as internal standard. MS spectra were made by Shimadzu QP-200 mass spectrometer. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using a benzene-ethyl acetate-diethylamine mixture (6:2:1 v/v/v) as the mobile phase.

Procedure for the Preparation of 4-Amino-1-aryl-4-chloro-2-(*N*,*N*-diethylamino)-2,4-diaza-1,3-butadiene (**3a**).

N-Phenyl-*N'*,*N'*-diethylurea (**1a**) (9.6 g, 0.05 mole), anhydrous toluene (70 ml) and PCl_5 (11.5 g, 0.055 mole) were gently heated at about 50 °C until the disappearance of the urea (TLC) was completed. Then the toluene and $POCl_3$ were removed using a rotary evaporator. The crude N^1,N^1-diethyl-N^2-chlorocarboxyamidine (**2a**) was dissolved in a new portion of anhydrous toluene (70 ml) and cyanamide (2.1 g, 0.05 mole) in anhydrous diethyl ether (5 ml) was added. The mixture was left for about 24 hours at room temperature. Then the toluene was removed in the rotary evaporator. The resulted oil was washed with anhydrous diethyl ether (50 ml) and neutralized with methanolic NaOH solution. A precipitate (inorganic salt) was filtered off, and the methanolic solution was evaporated. The oily product **3a** (10.6 g, 84%) was chromatographically pure: R_f: 0.68; ^{1}H nmr: δ 1.06 (t, 6H, N(CH_2CH_3)$_2$), 3.35 (q, 4H, N(CH_2CH_3)$_2$), 6.80-7.48 (m, 2H (NH_2), 5H$_{arom}$); uv: λ_{max} (ε*10^{-3}) (methanol): 209.4 (30.12), 240.2 (16.62).

Anal. Calcd. for $C_{12}H_{17}N_4Cl$: C, 57.02; H, 6.79; N, 22.15. Found: C, 57.60; H, 6.84; N, 22.40.

General Procedure for the Preparation of 4-Amino-2-(*N*,*N*-diethylamino)-(6,7)-R-substituted quinazolines (**4a-4g**).

The crude N^1,N^1-diethyl-N^2-chlorocarboxyamidine (**2**) (0.05 mole), prepared from the appropriate *N*-(3(4)-R-phenyl)-*N'*,*N'*-diethylurea (**1**) according to the procedure described in the synthesis of **3a** was dissolved in a portion of anhydrous toluene (70 ml). Then cyanamide (2.1 g, 0.05 mole) in anhydrous diethyl

ether (5 ml) was added there. The mixture was left for 1 hour, and then, $TiCl_4$ (5 ml, 0.05 mole) in anhydrous toluene (20 ml) was gradually added. The agitation was continued at 50 °C for 3 h. Solvents were removed using a rotary evaporator and the resulting gluey solid was washed with toluene and 20% aqueous NaOH (100 ml) was added. After a rapid decomposition the mixture was immediately extracted with toluene in order to avoid a hydrolysis to 3,4-dihydro-2-(*N,N*-diethylamino)-4-quinazolones. Purified and dried (calcium chloride) compounds (**4**) were crystallized from ethanol or acetone. In the case of difficulties in crystallization the compounds were chromatographed on silica gel (benzene-ethyl acetate mixture 3:1 v/v).

4-Amino-2-(*N,N*-diethylamino)quinazoline (**4a**).

This compound was obtained in 71% yield; mp: 73-74 °C; R_f: 0.50; ^{1}H nmr: δ 1.08 (t, 6H, $N(CH_2CH_3)_2$), 3.34 (q, 4H, $N(CH_2CH_3)_2$), 6.91 (s, 1H, NH), 7.22 (dd, *J* = 7.5 Hz, 2H, H-6, 7), 7.47 (d, *J* = 7.5 Hz, 2H, H-5, 8), 8.12 (s, 1H, NH) ppm; ^{13}C nmr: δ 9.44 (CH_3), 37.14 (CH_2), 115.28 (C-4a), 118.30 (C-5), 124.31 (C-6), 125.27 (C-8), 135.12 (C-7), 142.44 (C-8a), 150.20 (C-2), 162.26 (C-4) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 289.2 (1.40), 238.9 (16.61); basic: 275.0 (3.27), 238.4 (15.41), 212.1 (20.65) nm; ms: m/z (%) 27 (28), 28 (26), 29 (69), 30 (51), 39 (12), 42 (17), 44 (65), 51 (17), 56 (14), 65 (16), 72 (100), 91 (13), 92 (12), 93 (17), 100 (73), 118 (24), 174 (31), 187 (13), 216 (M^+, 40); pK_a = 7.79 ± 0.15 (λ_{anal} = 236 nm); k_I = 6.12 (±0.84)*10^{-5} s^{-1} (λ_{anal} = 238 nm).

Anal. Calcd. for $C_{12}H_{16}N_4$: C, 66.64; H, 7.47; N, 25.89. Found: C, 66.80; H, 7.41; N, 25.67.

4-Amino-6-methoxy-2-(*N,N*-diethylamino)quinazoline (**4b**).

This compound was obtained in 45% yield; mp: 218-220 °C; R_f: 0.70. ^{1}H nmr: δ 1.16 (t, 6H, $N(CH_2CH_3)_2$), 3.54 (q, 4H, $N(CH_2CH_3)_2$), 3.73 (s, 3H, OCH_3), 6.62 (s, 1H, NH), 6.99 (s, 1H, H-5), 7.13 (d, *J* = 9.0 Hz, 1H, H-7), 7.23 (d, *J* = 9.0 Hz, 2H, H-8), 8.38 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 255.3 (26.00), 201.0 (36.51), basic: 254.9 (26.00), 213.0 (14.80), 206.9 (11.00) nm; ms: m/z (%) 28 (17), 29 (20), 40 (11), 42 (16), 51 (14), 72 (100), 174 (36), 175 (66), 204 (27), 217 (54), 230 (12), 246 (M^+, 25); pK_a = 7.82 ± 0.09 (λ_{anal} = 251 nm).

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.38; H, 7.38; N, 22.73. Found: C, 64.03; H, 7.21; N, 22.96.

4-Amino-7-methoxy-2-(*N,N*-diethylamino)quinazoline (**4c**).

This compound was obtained in 39% yield; mp: 216-217 °C; R_f: 0.64; ^{1}H nmr: δ 1.17 (t, 6H, $N(CH_2CH_3)_2$), 3.51 (q, 4H, $N(CH_2CH_3)_2$), 3.78 (s, 3H, OCH_3), 6.82 (s, 1H, NH), 6.90-7.60 (m, 3H, H-5,6,8), 8.32 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 278.8 (7.00), 243.6 (23.39), 204.0 (24.92), basic: 273.9 (5.64), 255.2 (16.03), 214.3 (13.44) nm; ms:m/z (%) 29 (18), 33 (80), 38 (86), 40 (31), 46 (64), 51 (17), 72 (100), 77 (12), 78 (11), 148 (14), 174 (27), 175 (23), 202 (19), 217 (76), 218 (20), 231 (18), 246 (M^+, 35), 247 (11); pK_a = 8.31 ± 0.05 (λ_{anal} = 255 nm).

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.38; H, 7.38; N, 22.73. Found: C, 62.96; H, 7.32; N, 22.60.

4-Amino-6-chloro-2-(*N,N*-diethylamino)quinazoline (**4d**).

This compound was obtained in 79% yield; mp; 126-128 °C; R_f: 0.65; ^{1}H nmr: δ 1.09 (t, 6H, $N(CH_2CH_3)_2$), 3.33 (q, 4H, $N(CH_2CH_3)_2$), 6.70 (s, 1H, NH), 6.99 (s, 1H, H-5), 7.25 (d, *J* = 8.7 Hz, 1H, H-7), 7.40 (s, 1H, H-5), 7.53 (d, *J* = 8.7 Hz, 1H, H-8), 8.25 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 243.8 (15.34), basic: 247.4 (13.79), 216.3 (14.05) nm; ms: m/z (%) 28 (21), 29 (61), 42 (18), 44 (56), 51 (15), 72 (100), 77 (12), 152 (14), 178 (65), 180 (32), 221 (15), 250 (M^+, 23); pK_a = 6.98 ± 0.17 (λ_{anal} = 271 nm).

Anal. Calcd. for $C_{12}H_{15}N_4Cl$: C, 57.48; H, 6.04; N, 22.33. Found: C, 56.98; H, 6.17; N, 22.20.

4-Amino-7-chloro-2-(*N,N*-diethylamino)quinazoline (**4e**).

This compound was obtained in 65% yield; mp: 120-122 °C; R_f: 0.58; ^{1}H nmr δ 1.10 (t, 6H, $N(CH_2CH_3)_2$), 3.35 (q, 4H, $N(CH_2CH_3)_2$), 6.80-7.60 (m, 4H, H-5,6,8, NH), 8.32 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 237.4 (12.67), 208.1 (21.34), basic: 261.0 (12.54), 215.4 (17.72) nm; ms: m/z (%) 29 (56), 32 (42), 42 (15), 44 (59), 51 (17), 64 (14), 72 (100), 74 (10), 77 (15), 100 (17), 152 (13), 178 (80), 180 (26), 210 (11), 221 (13), 234 (12), 250 (M^+, 30), 252 (10); pK_a = 7.09 ± 0.12 (λ_{anal} = 261 nm).

Anal. Calcd. for $C_{12}H_{15}N_4Cl$: C, 57.48; H, 6.04; N, 22.33. Found: C, 57.05; H, 5.94; N, 22.90.

4-Amino-6-nitro-2-(*N,N*-diethylamino)quinazoline (**4f**).

This compound was obtained in 26% yield; mp: 148-150 °C; R_f: 0.38; ^{1}H nmr: δ 1.07 (t, 6H, $N(CH_2CH_3)_2$), 3.37 (q, 4H, $N(CH_2CH_3)_2$), 6.62 (s, 1H, NH), 6.99 (s, 1H, H-5), 7.13 (d, *J* = 9.0 Hz, 1H, H-7), 7.23 (d, *J* = 9.0 Hz, 2H, H-8), 8.90 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 290.5 (15.44), 216.9 (13.79), basic: 322.0 (12.58), 216.5 (13.63) nm; ms: m/z (%) 46 (27), 51 (13), 65 (11), 72 (100), 163 (17), 189 (55), 190 (27), 219 (20), 232 (64), 246 (30), 261 (M^+, 51); pK_a = 6.05 ± 0.08 (λ_{anal} = 270 nm).

Anal. Calcd. for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.80; N, 26.79. Found: C, 55.30; H, 5.70; N, 26.43.

4-Amino-7-nitro-2-(*N,N*-diethylamino)quinazoline (**4g**).

This compound was obtained in 12% yield; mp: 164-166 °C; R_f: 0.27; ^{1}H nmr: δ 1.05 (t, 6H, $N(CH_2CH_3)_2$), 3.76 (q, 4H, $N(CH_2CH_3)_2$), 7.20-8.40 (m, 4H, H-5,6,8, NH), 10.01 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 243.0 (17.79), basic: 254.0 (16.19), 214.7 (13.84) nm; ms: m/z (%)51 (12), 72 (100), 100 (14), 118 (11), 163 (15), 189 (64), 219 (21), 232 (48), 245 (17), 261 (M^+, 25); pK_a = 5.99 ± 0.21 (λ_{anal} = 269 nm).

Anal. Calcd. for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.80; N, 26.79. Found: C, 54.96; H, 5.97; N, 26.49.

2-(*N,N*-Diethylamino)-4-(*N,N*-dimethylamino)quinazoline (**6a**).

This compound was synthesized according to the procedure given in [7]. Yield: 79%; mp: 125-127 °C; R_f: 0.64; pK_a = 8.88 ± 0.09 (λ_{anal} = 279 nm); k_{II} =6.52(±0.34)*$10^{-6}$$s^{-1}$ (λ_{anal}=289 nm).

Procedures for the Preparation of 3,4-Dihydro-2-(*N,N*-diethylamino)-4-quinazolone (**5a**).

Procedure A.

The sediment resulted from the reaction of the crude *N*^{1},*N*^{1}-diethyl-*N*^{2}-chlorocarboxyamidine (**2**) with cyanamide, and $TiCl_4$ was treated with 20% HCl (100 ml) and left for 24 hours at room temperature. The suspension was filtered off and the solution was alkalized with 20% NaOH. The precipitate was extracted with toluene (100 ml). The combined extracts were dried over $CaCl_2$ and concentrated. The product (**5a**) was crystallized from acetone.

Procedure B.

2-(*N,N*-Diethylamino)-4-(*N,N*-dimethylamino)quinazoline (**6a**) (0.3 g, 1.25 mmole) was dissolved in 5% aqueous HCl (30 ml). The mixture was kept at the temperature of 80 °C for 5 days untill

the disappearance of starting quinazoline was completed. Then it was cooled down and 5% aqueous NaOH solution (30 ml) was added yielding a precipitate that was extracted with toluene (100 ml). Extracts were dried over $CaCl_2$, concentrated and the product (**5a**) was crystallized from acetone as white crystalls. Yield (A): 76%; (B) 95%; mp: 164-165 °C; R_f: 0.13. ^{1}H nmr: δ 1.13 (t, 6H, $N(CH_2CH_3)_2$), 3.56 (q, 4H, $N(CH_2CH_3)_2$), 7.07 (dd, *J* = 7.5, 6.9 Hz, 1H, H-6), 7.22 (d, *J* = 7.5 Hz, 1H, H-5), 7.55 (dd, *J* = 7.5, 6.9 Hz, 1H, H-7), 7.88 (d, *J* = 7.5 Hz, H-8), 11.06 (s, 1H, NH) ppm; uv: λ_{max} ($\varepsilon*10^{-3}$) acidic: 308.9 (3.08), 233.7 (41.65), 207.7 (18.83), basic: 341.1 (3.89), 275.9 (19.25), 252.8 (25.22), 235.1 (31.29), 212.0 (33.64) nm; ms: m/z (%) 63 (14), 64 (11), 72 (50), 90 (43), 91 (10), 92 (10), 117 (14), 119 (17), 132 (11), 145 (43), 146 (18), 171 (13), 174 (41), 188 (100), 189 (15), 217 (M^+, 46).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.33; H, 6.97; N, 19.33. Found: C, 66.05; H, 7.09; N, 19.23.

Determination of the Hydrolysis Rates of (**4a**) and (**6a**) quinazolines.

The appropriate quinazoline (0.53mmole) was dissolved in 50 ml of methanol. Then 2 ml of the standard solution was dilluted with 5% HCl in 50 ml measuring flask. Such solution was kept at the temperature of 80 °C for 3 h. Samples taken in regular intervals were analyzed by the spectrophotometric method.

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REFERENCES AND NOTES

[1] D. W. Fry, A. J. Kraker, A. McMichael, L. A. Ambroso, J. M. Nelson, W. R. Leopold, R. W. Connors and A. J. Bridges, *Science*, **265**, 1093 (1994).

[2] T. M. Traxler, P. Furet, H. Melt, E. Buchdunger, T. Meyer and N. Lydon, *J. Med. Chem.*, **39**, 2289 (1996).

[3] J. B. Hynes, A. Tomazic´, A. Kumar, V. Kumar and J. H. Freisheim, *J. Heterocyclic Chem.*, **28**, 1981 (1991).

[4] N. V. Harris, C. Smith and K. Bowden, *J. Med. Chem.*, **27**, 7 (1992).

[5] H. Meerwein, P. Laasch, R. Mersch and J. Nentwig, *Chem. Ber*., **89**, 224 (1956).

[6] V. Gomez Parra, R. Madronero and S. Vega, *Synthesis*, **1977**, 345.

[7] W. Zielin´ski, A. Kudelko and E. M. Holt, *Heterocycles*, **48**, 319 (1998).

[8] A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, **64**, 667 (1931).

[9] W. Zielin´ski and M. Mazik, *Polish J. Chem.*, **68**, 489 (1994).

[10] J. R. Keneford, J. S. Morley, J. C. Simpson and P. H. Wright, *J. Chem. Soc*., **1950**, 1104.

[11] B. E. Christensen and A. J. Tomisek, *J. Am. Chem. Soc*., **68**, 1306 (1946).

[12] W. Dymek and D. Sybistowicz, *Monatsh. Chem*., **96**, 542 (1965).

[13] E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).

[14] A. Albert and E. P. Serjeant, Ionization Constants of Acids and Bases, London: Methuen & Co Ltd, New York: J. Wiley&Sons, 1962, p 69.

[15] J. Shorter, Correlation Analysis in Organic Chemistry, Clarendon Press, Oxford, 1973.

[16] M. Charton, *J. Org. Chem.*, **30**, 3341 (1965).

[17] M. Dewar and R. Dougherty, The PMO Theory of Organic Chemistry, New York 1975, pp 99-110.

[18] W. Zielin´ski and A. Kudelko, *Monatsh.Chem*., **131**, 895 (2000).

[19] W. Zielin´ski and A. Kudelko, *Monatsh.Chem*., **131**, 733 (2000).