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Synthesis and Basicity of 4-Amino-2-phenylquinazolines

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Summary. A new group of 6- and 7-substituted compounds of 4-amino-2-phenylquinazoline were synthesized by reaction of N-arylbenzimidoyl chlorides with cyanamide in the presence of $TiCl_4$. The products were identified by spectroscopic methods, their dissociation constants were determined and are discussed.

Keywords. 4-Amino-2-phenylquinazolines; UV/Vis spectroscopy; NMR spectroscopy; pK_a values; Tautomerism.

Introduction

Earlier investigations on the synthesis of aminoquinazoline derivatives have confirmed that methods using N-arylbenzimidoyl chlorides may be efficiently applied for the preparation of new quinazoline derivatives of potential biological activity [1–3]. Many methods exist for the generation of 4-aminoquinazolines, the most popular one being the nucleophilic transformation of the appropriate 4-substituted quinazolines with ammonia [4] or amines [5]. Other methods start from *o*-aminobenzonitriles and proceed *via* cyclization [6] or cross-dimerization reactions [7]. In this paper we report on the synthesis of 6- and 7-substituted 4-amino-2-phenylquinazolines by reaction of N-arylbenzimidoyl chlorides with cyanamide. Bearing in mind that acid-base interactions are of importance for the pharmacological activity of the title compounds, their pK_a values have also been determined.

Results and Discussion

The presented synthetic pathway originates from *Meerwein*'s report on the reaction of N-phenylbenzimidoyl chloride with some nitriles [8] and from our method for the preparation of 4-N,N-dimethylaminoquinazoline derivatives [9]. N-Arylbenzamides (**1**) were reacted with PCl_5 in benzene at elevated temperatures to afford the corresponding N-arylbenzimidoyl chlorides (**2**). These were treated with cyanamide at room temperature, yielding 1-amino-4-aryl-1-chloro-3-phenyl-2,4-diaza-1,3-butadienes (**3**) as intermediates. After several hours of heating in benzene

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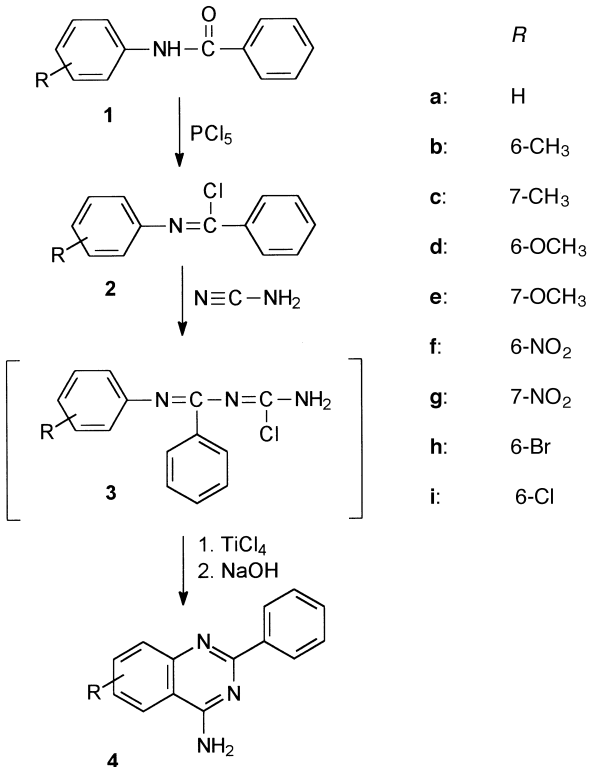
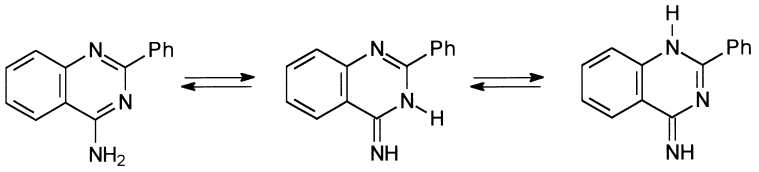


Scheme 1

in presence of the *Lewis* acid catalyst $TiCl_4$, **3** underwent cyclization to highly stable quinazoline-catalyst complexes ($\mathbf{4} \cdot TiCl_4$).

As acid catalyzed decomposition of the quinazoline-catalyst complexes afforded mainly 2-phenyl-4-quinazolones, their hydrolysis was effected by concentrated NaOH. To avoid rapid consecutive hydrolysis of **4** to the corresponding quinazolones ($k = 2 \cdot 10^{-4}$ s^{-1}), which proceeds about 50 times faster in systems without a substituent at the amino nitrogen atom compared with substituted derivatives [9], the products were immediately extracted with benzene. Thus we obtained eight new derivatives of 4-amino-2-phenylquinazoline substituted at positions 6 and 7 (**4b–i**) Their structure was confirmed by spectroscopic and elementary analysis. The yields of the products varied considerably due to difficulties of isolation and – mainly – because of the hydrolysis of **4** to the corresponding quinazolones. An influence of the substituent type on the yields could also be explained on the basis of the above mentioned process.

The determination of the dissociation constants of **4a–i** was performed according to the spectrophotometric method of *Albert* and *Serjeant* [10] in 50% aqueous methanol solution (10^{-5} *M*, room temperature). The absorptions maxima of the quinazoline ions were selected as analytical wavelengths, bearing in mind their considerable shifts relative to the maxima of the non-protonated forms. The results show that electron-donating groups in positions 6 or 7 of the quinazoline ring cause an increase in basicity compared with the pK_a value of the parent compound **4a** ($R = H$); the opposite holds for electron-withdrawing groups. Generally, 4-amino-2-



Scheme 2

phenylquinazolines are weaker bases than the corresponding 4-N,N-dimethylamino-2-phenylquinazolines ($pK_a = 4.42$–6.61) [11]. According to MNDO calculations, the amino group remains rather untwisted in the ring plane (twist angle: 11.3°), thus enabling the free electron pair of the amino nitrogen atom to couple with the π electrons of the aromatic system. In spite of resonance and inductive phenomena, the steric effect resulting from the twist of the bulky dimethylamino group (twist angle: 73.3°) is not strong enough to cause a decrease in basicity. A different behaviour was observed in the case of 1-amino- ($pK_a = 7.27$) and 1-N,N-dimethylamino-3-methyl-isoquinoline ($pK_a = 6.29$) where the secondary steric effect connected with the twisting of the dimethylamino group from the ring plain indeed leads to a decrease in basicity originating from electron coupling limitations [12]. According to this it is supposed that there are additional effects influencing the electron effect transfer in the systems under consideration. The ^{1}H NMR spectra of **4b–e** show two singlets for the NH groups at low field. On account of these observation we conclude that a tautomerism between amino and imino forms (Scheme 2) might be responsible for the considerable changes in basicity.

In contrast to 4-amino-2-phenylquinazolines with electron-donating substituents which mainly occur in the imino form, quinazolines with electron-withdrawing substituents (**4f–i**) occur both in the amino (broad singlet at higher field) and the imino forms (singlet at low field). Up to now it has been assumed from UV spectroscopic evidences that aminoquinazolines do not exist in the imino form [3, 13]. This investigation has shown that the problem is more complicated and that tautomeric equilibria cannot be excluded in the title compounds.

Experimental

UP spectra were recorded with a Shimadzu UV-2102 spectrophotometer, basic medium: 0.05 *M* NaOH in 50% aqueous methanol, acidic medium: 0.05 *M* HCl in 50% aqueous methanol. Absorption mixima of the quinazoline ions (B-band) were selected as analytical wavelenghts. Elementary analyses were carried out with a Perkin-Elmer 240c analyzer their results were in satisfactory agreement with the calculated values. ^{1}H NMR spectra were recorded on a Varian Inova 300 at 300 MHz spectrometer in *DMSO*-d_6 solutions. MS spectra run on a Shimadzu QP-200 mass spectrometer. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using benzene: ethyl acetate = 3:1 (v/v) as the mobile phase.

4-Amino-2-phenyl-6,7-substituted quinazolines (**4-i**); *general procedure*

The appropriate N-arylbenzamide (**1**, 0.05 mol), anhydrous benzene (70 cm^3), and PCl_5 (11.5 g, 0.055 mol) were gently heated at about 50°C until **1** had disappeared completely (TLC). Then benzene and $POCl_3$ were removed using a rotary evaporator. The crude N-arylbenzimidoyl chloride (**2**) was dissolved in 70 cm^3 anhydrous benzene, and cyanamide (2.1 g, 0.05 mol) in anhydrous

diethyl ether (5 cm^3) was added. The mixture was left for 1-2 h; then, $TiCl_4$ (5 cm^3, 0.05 mol) in anhydrous benzene was gradually added, and agitation was continued at 50°C for about 3 h. The solvent was decanted from the resulting gluey solid (salts of 4-aminoquinazolines), and 100 cm^3 of 20% aqueous NaOH were added. After the rapid decomposition reaction had subsided, the mixture was immediately extracted with benzene in order to avoid a hydrolysis to 2-phenyl-4-quinazolones.

The combined extracts were dried over $MgSO_4$ and concentrated yielding an oily residue to which 50 cm^3 of methanol and 1 g of decolorizing charcoal were added followed by boiling under reflux (5 min). After filtration, the methanol was removed using a rotary evaporator, and compounds **4** were crystallized from ethanol or acetone. In case of difficulties with respect to crystalization, the quinazolines were converted to their hydrochlorides by saturation with gaseous HCl.

4-Amino-2-phenylquinazoline (**4a**; $C_{14}H_{11}N_3$)

Yield: 33.0%; m.p.: 146–147°C (Refs. [14, 15]); $R_f = 0.47$; ^{1}H NMR: $\delta = 5.80$ (1H, br s, NH_2), 7.14 (1H, dd, H-4′, $J = 7.5$, 7.5 Hz) 7.36 (2H, dd, H-3′,5′, $J = 7.5$, 6.9 Hz), 7.48–7.57 (3H, m, H-5,6,7), 7.68 (1H, d, H-8, $J = 8.7$ Hz), 7.92 (2H, d, H-2′,6′, $J = 6.9$ Hz), 10.20 (1H, s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 201.9 (41.25), 261.2 (14.84), 315.5 (8.90) nm (acidic); 215.4 (13.52), 261.9 (12.79), 316.0 (7.00) nm (basic); MS: *m/z* (%) = 221 (M^+, 100); $pK_a = 5.44 \pm 0.23$.

6-Methyl-4-amino-2-phenylquinazoline (**4b**; $C_{15}H_{13}N_3$)

Yield: 34.5%; m.p.: 260–261°C (**4b** · H_2O · HCl); $R_f = 0.56$; ^{1}H NMR: $\delta = 2.50$ (3H, s, CH_3), 7.64–7.77 (3H, m, H-3′,4′,5′), 7.90 (1H, d, H-7, $J = 8.4$ Hz) 8.19 (1H, d, H-8, $J = 8.4$ Hz), 8.36 (1H, s, H-5), 8.40 (2H, d, H-2′, 6′, $J = 7.2$ Hz), 9.72 (1H, br s, NH), 9.78 (1H, br s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 209.1 (35.35), 266.5 (35.19), 325.1 (10.31) nm (acidic); 213.4 (19.65), 251.8 (37.56), 303.7 (13.53) nm (basic); MS: *m/z* (%) = 235 (M^+, 100); $pK_a = 5.16 \pm 0.18$.

7-Methyl-4-amino-2-phenylquinazoline (**4c**; $C_{15}H_{13}N_3$)

Yield: 31.0%; m.p.: 245–246°C (**4c** · H_2O · HCl); $R_f = 0.45$; ^{1}H NMR: $\delta = 2.49$ (3H, s, CH_3), 7.60 (1H, d, H-6), $J = 8.7$ Hz) 7.65 (2H, dd, H-3′,5′, $J = 6.9$, 7.2 Hz), 7.71 (1H, dd, H-4′, $J = 7.2$, 7.2 Hz), 7.78 (1H, s, H-8), 8.22 (1H, d, H-5, $J = 8.7$ Hz), 8.32 (2H, d, H-2′6′, $J = 6.9$ Hz), 9.70 (1H, br s, NH), 9.80 (1H, br s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 212.8 (22.90), 253.3 (38.68), 303.7 (12.28) nm (acidic); 208.4 (34.49), 264.0 (33.90), 316.0 (10.00) nm (basic); MS: *m/z* (%) = 235 (M^+, 100); $pK_a = 5.53 \pm 0.11$.

6-Methoxy-4-amino-2-phenylquinazoline (**4d**; $C_{15}H_{13}N_3O$)

Yield: 25.5%; m.p.: 235–236°C (**4d** · H_2O · HCl); $R_f = 0.10$; ^{1}H NMR: $\delta = 3.99$ (3H, s, CH_3), 7.60–7.76 (4H, m, H-7,3′,4′,5′), 7.80 (1H, s, H-5), 7.92 (1H, d, H-8, $J = 9.0$ Hz) 8.30 (2H, d, H-2′,6′, $J = 7.2$ Hz), 9.60 (1H, br s, NH) 9.72 (1H, br s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 212.4 (30.49), 268.3 (33.55), 340.2 (10.40) nm (acidic); 214.4 (25.46), 250.7 (35.43), 304.1 (14.90) nm (basic); MS: *m/z* (%) = 251 (M^+, 100); $pK_a = 5.33 \pm 0.08$.

7-Methoxy-4-amino-2-phenylquinazoline (**4e**; $C_{15}H_{13}N_3O$)

Yield: 36.0%; m.p.: 230–232°C (**4e** · H_2O · HCl); $R_f = 0.50$; ^{1}H NMR: $\delta = 3.96$ (3H, s, CH_3), 7.36 (1H, d, H-6, $J = 9.0$ Hz) 7.65–7.77 (4H, m, H-8,3′,4′,5′) 8.41 (2H, d, H-2′,6′, $J = 6.9$ Hz), 8.45 (1H, d, H-5, $J = 9.0$ Hz), 9.56 (1H, br s, NH), 9.70 (1H, br, s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 211.0 (28.39), 255.2 (42.73), 322.1 (14.72) nm (acidic); 211.9 (21.45), 250.6 (46.54), 308.9 (11.97) nm (basic); MS: *m/z* (%) = 251 (M^+, 100); $pK_a = 5.62 \pm 0.07$.

6-Nitro-4-amino-2-phenylquinazoline (**4f**; $C_{14}H_{10}N_4O_2$)

Yield: 41.5%; m.p.: 193–195°C; $R_f = 0.29$; ^{1}H NMR: $\delta = 5.40$ (1H, br s, NH_2), 7.57 (2H, dd, H-3′,5′, $J = 7.2$, 7.2 Hz) 7.65 (1H, dd, H-4′, $J = 7.2$, 7.2 Hz), 7.91 (1H, s, H-5), 7.98 (2H, d, H-2′,6′, $J = 7.2$ Hz), 8.07 (1H, d, H-7, $J = 9.3$ Hz), 8.28 (1H, d, H-8, $J = 9.3$ Hz), 10.80 (1H, s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 225.2 (13.72), 320.8 (17.48) nm (acidic); 214.6 (17.65), 323.6 (15.82) nm (basic); MS: *m*/*z*(%) = 266 (M^+, 55); $pK_a = 4.54 \pm 0.27$.

7-Nitro-4-amino-2-phenylquinazoline (**4g**; $C_{14}H_{10}N_4O_2$)

Yield: 50.5%; m.p.: 138–140°C; $R_f = 0.41$; ^{1}H NMR: $\delta = 5.20$ (1H, br s, NH_2), 7.57 (1H, dd, H-4′ $J = 6.9$, 6.9 Hz) 7.64 (2H, dd, H-3′,5′, $J = 6.9$, 6.9 Hz), 7.97 (1H, d, H-5, $J = 8.4$ Hz), 8.01 (2H, d, H-2′,6′, $J = 6.9$ Hz), 8.22 (1H, d, H-6, $J = 8.4$ Hz), 8.83 (1H, s, H-8), 10.76 (1H, s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 211.3 (20.00), 259.0 (25.42) nm (acidic); 211.0 (18.12), 261.1 (26.38) nm (basic); MS: *m*/*z*(%) = 266 (M^+, 43); $pK_a = 4.27 \pm 0.32$.

6-Bromo-4-amino-2-phenylquinazoline (**4h**; $C_{14}H_{10}N_3Br$)

Yield: 82.5%; m.p.: 188–190°C (**4h**; $H_2O \cdot HCl$); $R_f = 0.65$; ^{1}H NMR: $\delta = 4.10$ (1H, br s, NH_2), 7.30–8.40 (8H, m), 11.10 (1H, s, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 201.0 (24.36), 225.5 (17.89), 235.3 (17.40) nm (acidic); 208.0 (16.76), 236.2 (20.5) nm (basic); MS: *m*/*z*(%) = 300 (M^+, 51); $pK_a = 4.78 \pm 0.08$.

6-Chloro-4-amino-2-phenylquinazoline (**4i**; $C_{14}H_{10}N_3Cl$)

Yield: 26.0%; m.p.: 230–231°C (**4i**; $H_2O \cdot HCl$); $R_f = 0.40$; ^{1}H NMR: $\delta = 4.55$ (1H, br s, NH_2), 7.25–780 (4H, m), 7.95 (2H, d, H-2′,6′, $J = 6.9$ Hz), 8.07 (1H, d, H-7, $J = 9.0$ Hz), 8.18 (1H, d, H-8, $J = 9.0$ Hz), 10.95 (1H, NH) ppm; UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) = 211.0 (32.03), 274.1 (23.38), 324.9 (8.58) nm (acidic); 214.2 (24.58), 253.6 (32.19), 302.1 (13.51) nm (basic); MS: *m*/*z*(%) = 255 (M^+, 100); $pK_a = 4.98 \pm 0.06$.

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