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HETEROCYCLIZATION OF QUINAZOL-2-YLGUANIDINES. 1. REACTION WITH AMINO ACIDS

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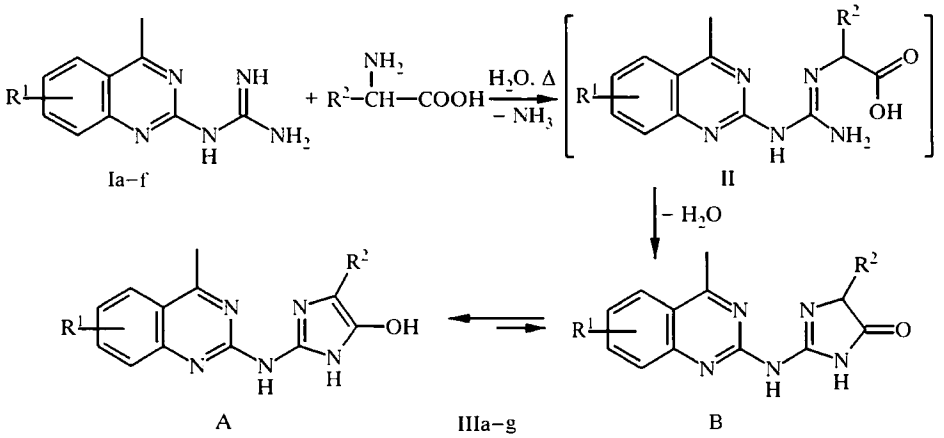
Condensation of 6(7)-R-4-methylquinazol-2-ylguanidines with α-amino acids produces 2-hydroxyimidazoles; with anthranilic acid, the corresponding 4-hydroxyquinazolines.

We discovered that 6(7)-R-4-methylquinazol-2-ylguanidines Ia-f condense readily with α-amino acids in boiling water. The reaction involves the guanidine moiety. Ammonia is released during the formation of the intermediate imino acids II, which cyclize with the release of water into the corresponding 5-hydroxy-2-[6(7)-R^1-4-methylquinazol-2-yl]amino-4-R^2-imidazoles IIIa-f. PMR spectra of IIIa-g (Table 1), which lack signals of the methylene or methine (for IIIg) protons of an imidazoline moiety, indicate that IIIa-g exist as the hydroxy (A) and not the oxo (B) isomers.



I - III a,g R^1 = H, b R^1 = 6-Me, c R^1 = 6-OMe, d R^1 = 6-OEt, e R^1 = 7-Me, f R^1 = 7-OMe, a-f R^2 = H, g R^2 = CH_2Ph

The reaction of 2-guanidinoquinazolines Ia-f with anthranilic acid gives analogous products. In this instance the cyclization products are the corresponding 4-hydroxy-2-[6(7)]-R-4-methylquinazol-2-yl]-aminoquinazolines IVa-f.

The existence of the 4-hydroxy isomers of IVa-f is consistent with the literature [1, 2] and is confirmed by the PMR spectra (Table 1), which contain a signal for only one NH proton and a signal for an OH group shifted to weak field and overlapped by a multiplet from aromatic protons.

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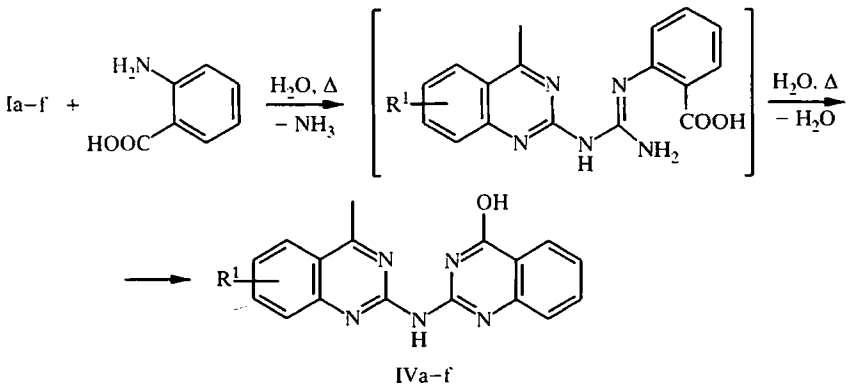
TABLE 1. PMR Spectra of Quinazolylaminoimidazoles IIIa-g and Quinazolylaminoquinazolines IVa-f

Compound	Chemical shift, δ, ppm
IIIa	2.75 (3H, s, 4'-CH_3); 3.68 (1H, s, OH); 7.3-8.0 (5H, m, H_{arom}); 8.10 (2H, br. s, NH)
IIIb	2.41 (3H, s, 6'-CH_3); 2.70 (3H, s, 4'-CH_3); 3.70 (1H, s, OH); 7.1-7.8 (4H, m, H_{arom}) 8.15 (2H, br. s, NH)
IIIc	2.80 (3H, s, 4'-CH_3); 3.58 (1H, s, OH); 3.95 (3H, s, 6'-OCH_3); 7.3-7.7 (4H, m, H_{arom}) 8.10 (2H, br. s, NH)
IIId	1.50 (3H, t, 6'-$OCH_2\underline{CH_3}$); 2.90 (3H, s, 4'-CH_3); 3.72 (1H, s, OH) 4.32 (2H, q, 6'-$O\underline{CH_2}CH_3$); 7.4-7.9 (4H, m, H_{arom}); 8.10 (2H, br. s, NH)
IIIe	2.40 (3H, s, 7'-CH_3); 2.72 (3H, s, 4'-CH_3); 3.68 (1H, s, OH); 7.1-7.8 (4H, m, H_{arom}) 8.10 (2H, br. s, NH)
IIIf	2.72 (3H, s, 4'-CH_3); 3.71 (1H, s, OH); 3.91 (3H, s, 7'-OCH_3); 6.9-7.9 (4H, m, H_{arom}) 8.10 (2H, br. s, NH)
IIIg	2.87 (3H, s, 4'-CH_3); 3.15 (1H, d, OH); 3.45 (2H, d, CH_2); 7.2-8.1 (9H, m, H_{arom}) 8.10 (2H, br. s, NH)
IVa	2.80 (3H, s, 4'-CH_3); 6.4-8.1 (9H, m, H_{arom}, OH); 8.30 (1H, br. s, NH)
IVb	2.40 (3H, s, 6'-CH_3); 2.75 (3H, s, 4'-CH_3); 6.4-7.8 (8H, m, H_{arom}, OH); 8.20 (1H, br. s, NH)
IVc	2.78 (3H, s, 4'-CH_3); 3.55 (3H, s, 6'-OCH_3); 6.4-7.9 (8H, m, H_{arom}, OH) 8.30 (1H, br. s, NH)
IVd	1.52 (3H, t, 6'-$OCH_2\underline{CH_3}$); 2.90 (3H, s, 4'-CH_3); 4.30 (2H, q, 6'-$O\underline{CH_2}CH_3$) 6.4-7.8 (8H, m, H_{arom}, OH); 8.30 (1H, br. s, NH)
IVe	2.35 (3H, s, 7'-CH_3); 2.80 (3H, s, 4'-CH_3); 6.4-7.7 (8H, m, H_{arom}, OH); 8.30 (1H, br. s, NH)
IVf	2.75 (3H, s, 4'-CH_3); 3.58 (3H, s, 7'-OCH_3); 6.4-7.9 (8H, m, H_{arom}, OH) 8.20 (1H, br. s, NH)



IV a R^1 = H, b R^1 = 6-Me, c R^1 = 6-OMe, d R^1 = 6-OEt, e R^1 = 7-Me, f R^1 = 7-OMe

The characteristics of the synthesized quinazolylaminoimidazoles IIIa-g and quinazolylaminoquinazolines IVa-f are given in Table 2.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 using methanol as eluent. PMR spectra were recorded on a Bruker AC-300 (300 MHz) instrument in DMSO-d_6 with TMS internal standard. Mass spectra were obtained on an LKB-9000 instrument with 70 eV ionizing-electron energy.

Starting 6(7)-R-4-methylquinazol-2-ylguanidines Ia-f were synthesized by the method [2].

TABLE 2. Characteristics of Quinazolylaminoimidazoles and Quinazolylaminoquinazolines

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		M^+	C	H	N		
IIIa	$C_{12}H_{11}N_5O$	241 / 241.25	59.75 / 59.57	4.56 / 4.71	29.05 / 28.93	244-246	56
IIIb	$C_{13}H_{13}N_5O$	255 / 255.27	61.18 / 61.31	5.10 / 5.03	27.45 / 27.32	269-271	66
IIIc	$C_{13}H_{13}N_5O_2$	271 / 271.27	57.56 / 57.37	4.80 / 4.66	25.83 / 26.00	>350	71
IIId	$C_{14}H_{15}N_5O_2$	285 / 285.31	58.95 / 58.90	5.26 / 5.38	24.56 / 24.46	244-246	55
IIIe	$C_{13}H_{13}N_5O$	255 / 255.27	61.18 / 61.34	5.10 / 4.92	27.45 / 27.37	199-201	81
IIIf	$C_{13}H_{13}N_5O_2$	271 / 271.27	57.56 / 57.47	4.80 / 4.94	25.83 / 25.77	258-260	70
IIIg	$C_{19}H_{17}N_5O$	330 / 330.37	69.09 / 69.21	4.85 / 4.72	21.21 / 21.30	234-236	27
IVa	$C_{17}H_{13}N_5O$	303 / 303.32	67.33 / 67.17	4.29 / 4.46	23.10 / 23.16	255-257	20
IVb	$C_{18}H_{15}N_5O$	317 / 317.35	68.14 / 68.29	4.73 / 4.60	22.08 / 22.23	205-207	50
IVc	$C_{18}H_{15}N_5O_2$	333 / 333.35	64.86 / 65.00	4.51 / 4.39	21.02 / 21.20	315-316	46
IVd	$C_{19}H_{17}N_5O_2$	347 / 347.37	65.71 / 65.88	4.90 / 4.83	20.17 / 20.18	198-200	37
IVe	$C_{18}H_{15}N_5O$	317 / 317.35	68.14 / 68.29	4.73 / 4.85	22.08 / 22.10	265-267	29
IVf	$C_{18}H_{15}N_5O_2$	333 / 333.35	64.87 / 65.00	4.51 / 4.39	21.02 / 21.13	224-226	41

5-Hydroxy-2-[6(7)-R-4-methylquinazol-2-yl]amino-4-R^2-imidazoles (IIIa-g). A mixture of the appropriate quinazolylguanidine (Ia-f, 0.01 mol) and an α-amino acid (0.012 mol) in water (100 ml) was boiled for 4-6 h and cooled. The precipitate of the compound III was filtered off and recrystallized from dioxane.

4-Hydroxy-2-[6(7)-R-4-methylquinazol-2-yl]aminoquinazolines (IVa-f). A mixture of the appropriate quinazolylguanidine (Ia-f, 0.01 mol) and anthranilic acid (0.01 mol) in DMSO (30 ml) was held at 100°C for 8-10 h, cooled, and poured into water. The precipitate of the compound IV was filtered off and recrystallized from dioxane.

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