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REACTIONS OF AMINOQUINOLINES WITH UNSATURATED CARBOXYLIC ACIDS. 3*. SYNTHESIS OF N-QUINOLYLASPARTIC ACIDS AND THEIR DERIVATIVES

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Reaction of aminoquinolines with maleic acid and its diethyl ester gave N-quinolylaspartic acids or their esters. In aqueous media 4-aminoquinoline formed a maleate or betaine. Hydrazides of aspartic acids were prepared, and N-(3- and 6-quinolyl)aspartic acids were converted into 5-carboxymethyl-1-quinolylimidazolidin-4-one-2-thiones.

Keywords: carboxymethylimidazolidinonethiones, dihydrazides, ethyl quinolylaspartates, N-quinolylaspartic acids.

Aromatic amines react with maleic acid and its diethyl ester to give a range of compounds – amides, maleimides, N-arylaspartic acids or their esters [2]. There are no literature data on the reaction of maleic acid with heterocyclic amines. The reported derivatives of N-pyridyl and N-furfurylaspartic acids [3, 4] were prepared by the reaction of monomethyl maleate with aminopyridine or furfurylamine derivatives.

We have studied the reactions of aminoquinolines **1a-g** with maleic acid or its diethyl ester (Scheme 1). N-Quinolylaspartic acids **2** were obtained by heating of aminoquinolines with maleic acid in water (except for **2b**) or toluene. In contrast to the 3-, 5-, 6-, and 8-aminoquinolines, 4-aminoquinoline did not give the product of nucleophilic addition with maleic acid in water, but instead salt **4b** which regenerated to the initial amine **1b** by treatment with sodium carbonate.

Diethyl esters of N-quinolylaspartic acids **3** were synthesized by heating amines **1** with diethyl maleate for 24-40 h at 120°C with acetic acid as catalyst. Esters **3** were isolated from the reaction mixtures by crystallization or by chromatography on a silica gel column. Alkaline hydrolysis of diethyl esters gave the free aspartic acids **2**.

4-Aminoquinoline was acylated with diethyl maleate in the presence of water to give 4-amino-1-(3-carboxylato-1-oxo-2-propen-1-yl)quinolinium betaine (**5b**) which was readily hydrolyzed to the initial amine **1b** with aqueous sodium hydrogen carbonate.

The ^{1}H NMR spectra (in CF_3COOH and DMSO-d_6) of aspartic acids **2** contained characteristic doublets of the methylene group protons in the range 2.50-3.10 ppm and multiplets or triplets of the methyne group protons in the range 4.30-4.80 ppm. The signals of the NH group protons appear in the 5.50-6.80 ppm range as a doublet or multiplet. The spectrum of betaine **5b** in DMSO-d_6 contains signals of the quinoline ring and a broad singlet at 6.68 ppm which corresponds to the methyne proton and the proton at $C_{(3)}$. The IR spectrum of betaine contains absorption bands at 1660 and 1570 cm^{-1} corresponding to the carbonyl group and carboxylate ion respectively.

Dihydrazides **7** were obtained by reaction of the N-quinolylaspartic acids and their esters with hydrazine. The reaction with esters was carried at room temperature but acids were heated in ethanol or dioxane.

* For Communication 2, see [1].

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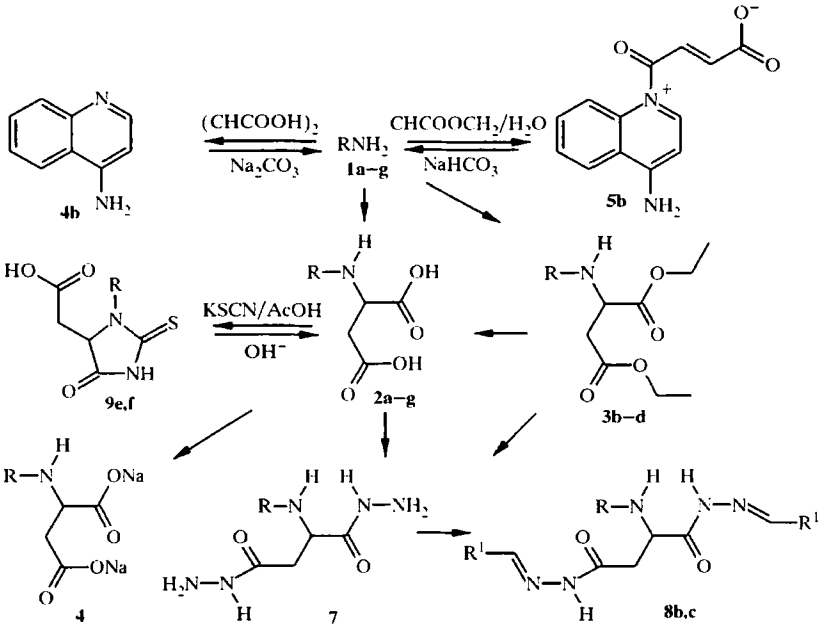
Formation of dihydrazides was confirmed by their reaction with 4-dimethylaminobenzaldehyde. Overlapping broad singlets of amino groups in the range 3.50-4.50 ppm and the characteristic signals of the imino group of the CONH units in the range 8.93-9.60 ppm were observed in the spectra of dihydrazides (in DMSO-d_6).



a R = 3-C_9H_6N; **b** R = 4-C_9H_6N; **c** R = 5-C_9H_6N; **d** R = 2-CH_3-5-C_9H_5N; **e** R = 6-C_9H_6N; **f** R = 2-CH_3-6-C_9H_5N; **g** R = 8-C_9H_6N. R^1 = 4-$(CH_3)_2N$-C_6H_4

Comparison of the ^{1}H NMR spectra of dihydrazides **7** and dibenzylidenedihydrazides **8** shows that two methyne singlets appear at 2.95 and 2.99 ppm appear in the latter. Benzene and quinoline multiplets overlap in the 6.30-8.60 ppm range.

5-Carboxymethyl-1-quinolylimidazolidin-4-on-2-thiones were obtained as their hydrochlorides by reaction of N-quinolylaspartic acids **2e,f** with potassium thiocyanate in acetic acid with subsequent addition of hydrochloric acid. Imidazolidinon-2-thiones were isolated by neutralization of the reaction mixture to decompose hydrochlorides after distillation of the excess acid. Imidazolidinon-2-thiones **9e,f** were converted into the initial aspartic acids **2e,f** by alkaline hydrolysis. No success was achieved in the synthesis of the corresponding 5-carboxymethyl-1-quinolyl-2,4-imidazolidindiones using urea or sodium cyanate.

N-Quinolylaspartic acids **2b,c,d,g**, like N-quinolyl-β-alanines [5] derived from 4-, 5-, or 8-aminoquinolines, did not undergo cyclization evidently because of amine-imine tautomerism and the presence of hydrogen bonds.

The ^{1}H NMR spectra of imidazolidinonthiones **9** (in DMSO-d_6) have signals of the methylene protons as an ABX system in the range 2.36-3.10 ppm and signals of the methyne group as a triplet at 5.25-5.31 ppm. The IR spectra of compounds **9** contain intense NH stretching bands at 3160 and 3460 cm^{-1}, intense bands in the 1790-1720 cm^{-1} ascribed to stretching vibrations of the carbonyl groups in the imidazolidine ring and the carboxylate groups. The presence of absorption bands in the 1250-1000 cm^{-1} region confirms the presence of the imidazolidine ring.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C, solvent	^{1}H NMR spectrum	
		C	H	N		solvent	δ, ppm (coupling constant, Hz)
1	2	3	4	5	6	7	8
2a	$C_{13}H_{12}N_2O_4$	59.88 / 60.00	4.64 / 4.65	10.77 / 10.76	236 (dec.), ethanol	DMSO-d_6	2.68-2.93 (m, CH_2); 4.30-4.65 (m, CH); 6.38-6.83 (m, NH); 7.04-8.65 (6H, m, arom.)
2b	$C_{13}H_{12}N_2O_4$	59.73 / 60.00	4.36 / 4.65	10.70 / 10.76	252 (dec.), ethanol	CF_3COOH	3.09 (d, J = 5, CH_2); 4.73-5.08 (m, CH); 6.55-8.18 (6H, m, arom.)
2c	$C_{13}H_{12}N_2O_4$	59.75 / 60.00	4.71 / 4.65	10.72 / 10.76	321 (dec.), ethanol	CF_3COOH	2.85 (d, J = 6, CH_2); 3.25 (t, J = 5, CH); 6.59-6.96 (6H, m, arom.)
2d	$C_{14}H_{14}N_2O_4$	60.93 / 61.31	4.81 / 5.14	9.94 / 10.21	229 (dec.), ethanol	DMSO-d_6	2.60 (s, CH_3); 2.85 (d, J = 7, CH_2); 4.09 (t, J = 7, CH); 6.34-8.62 (5H, m, arom.)
2e	$C_{13}H_{12}N_2O_4$	59.58 / 60.00	4.63 / 4.65	10.81 / 10.76	295 (dec.), ethanol	CF_3COOH	2.67-3.25 (m, CH_2); 4.35-4.79 (m, CH); 6.76-8.54 (6H, m, arom.)
2f	$C_{14}H_{14}N_2O_4$	61.22 / 61.31	5.20 / 5.15	10.27 / 10.21	307.5 (dec.), ethanol	DMSO-d_6	2.52 (s, CH_2); 2.55-2.84 (m, CH_2); 4.20-4.52 (m, CH); 6.60-7.74 (6H, m, arom.)
2g	$C_{13}H_{12}N_2O_4$	60.30 / 60.00	4.96 / 4.65	11.13 / 10.76	212 (dec.), ethanol	DMSO-d_6	3.31 (d, J = 6.5, CH_2); 4.44-4.71 (m, CH); 6.59-9.00 (7H, m, NH, arom.)

TABLE 1 (continued)

1	2	3	4	5	6	7	8
3b	$C_{17}H_{20}N_2O_4$	64.47 / 64.54	6.33 / 6.37	8.85 / 8.86	153-154, ethanol	$CDCl_3$	1.21 (t, J = 7, $CHCOOCH_2\underline{CH_3}$); 1.25 (t, J = 7, $CHCOOCH_2\underline{CH_3}$); 2.98 (d, J = 4.2, CH_2CO); 4.13 (q, J = 6.5, $CH_2COO\underline{CH_2}$); 4.23 (q, J = 6.5, $CHCOO\underline{CH_2}$); 4.45-4.73 (m, CH); 6.11 (d, J = 8, NH); 6.33-8.60 (6H, m, arom.)
3c	$C_{17}H_{20}N_2O_4$	64.40 / 64.54	6.28 / 6.37	8.72 / 8.86	74-75, hexane	$CDCl_3$	1.15 (t, J = 7, $2CH_3$); 2.92 (d, J = 5, CH_2CO); 4.12 (q, J = 6.8, $CH_2COO\underline{CH_2}$); 4.20 (q, J = 6.8, $CHCOO\underline{CH_2}$); 4.43-4.72 (m, CH); 5.53 (d, J = 8, NH); 6.50-8.85 (6H, m, arom.)
3d	$C_{18}H_{22}N_2O_4$	65.29 / 65.44	6.62 / 6.71	8.31 / 8.48	77.5-78.5, hexane	$CDCl_3$	1.18 (t, J = 6.5, $2CH_3$); 2.64 (s, 2-CH_3); 2.92 (d, J = 5.8, CH_2CO); 4.14 (q, J = 6, $CH_2COO\underline{CH_2}$); 4.22 (q, J = 6, $CHCOO\underline{CH_3}$); 4.59-4.80 (m, CH); 5.42 (d, J = 8, NH); 6.48-8.21 (5H, m, arom.)
4b	$C_{13}H_{12}N_2O_4$	59.39 / 60.00	4.86 / 4.65	10.57 / 10.76	198.5-199.5, ethanol	DMSO-d_6	6.15 (s, CH=CH); 6.85 (d, J = 6, 3-H); 7.55-9.16 (7H, m, NH_3^+, arom.)
5b	$C_{13}H_8N_{10}O_3$	64.65 / 64.46	4.43 / 4.16	11.54 / 11.56	212-213, ethanol	DMSO-d_6	6.68 (s, 3-H, CH=CH); 7.35-8.47 (5H, m, arom.)
6b	$C_{13}H_{10}N_2O_4Na_2$	50.96 / 51.33	3.18 / 3.31	9.33 / 9.21	379 (dec.)	D_2O	2.85 (m, CH_2); 4.37 (m, CH); 6.32-8.33 (6H, m, arom.)
6b$_1$	$C_{13}H_{10}N_2O_4K_2$	46.01 / 46.41	3.10 / 3.02	8.42 / 8.32	360 (dec.)		
6b$_2$	$C_{13}H_{10}N_2O_4Li_2$	57.43 / 57.38	3.80 / 3.70	10.22 / 10.29	369 (dec.)		

TABLE 1 (continued)

1	2	3	4	5	6	7	8
6d	$C_{14}H_{12}N_2O_4Na_2$	52.57 52.84	3.68 3.80	8.95 8.80	355 (dec.)	D_2O	2.51 (s, CH_2); 2.82 (s, CH_2); 4.21 (m, CH); 6.00-8.38 (5H, m, arom.)
6e	$C_{13}H_{10}N_2O_4Na_2$	51.04 51.33	3.15 3.31	9.15 9.21	340 (dec.)	D_2O	2.88 (d, J = 6, CH_2); 4.26 (m, CH); 6.73-8.49 (6H, m, arom.)
6f	$C_{14}H_{12}N_2O_4Na_2$	52.70 52.84	3.59 3.80	8.70 8.80	360 (dec.)	D_2O	2.51 (s, CH_3); 2.83 (q, J = 7, CH_2); 4.32 (t, J = 6, CH); 6.61-7.96 (5H, m, arom.)
7b	$C_{13}H_{16}N_6O_2$	53.88 54.16	5.40 5.59	28.97 29.15	197.5-198.5, ethanol	DMSO-d_6	2.50-2.75 (m, CH_2); 3.85-4.24 (s, NH_2); 4.28-4.68 (m, CH); 6.39-8.45 (7H, m, arom.); 8.93-9.60 (m, 2CONH)
7d	$C_{14}H_{18}N_6O_2$	55.63 55.99	5.19 5.37	27.66 27.98	224.5-226, ethanol	DMSO-d_6	2.53-2.76 (m, CH_2); 3.18-3.95 (m, $2NH_2$); 4.19-4.58 (m, CH); 6.18-8.58 (6H, m, NH, arom.); 8.85-9.55 (m, 2CONH)
7e	$C_{13}H_{16}N_6O_2$	53.95 54.16	5.36 5.59	28.89 29.15	210 (dec.), ethanol	DMSO-d_6	2.30-2.58 (m, CH_2); 3.41-4.17 (m, $2NH_2$); 4.25-4.55 (m, CH); 6.18 (d, J = 8, NH); 6.65-8.55 (6H, m, arom.); 8.85-9.44 (m, 2CONH)
8b	$C_{31}H_{34}N_8O_2$	67.28 67.62	5.93 6.22	20.11 20.35	223-224, ethanol	DMSO-d_6	2.40-2.60 (m, CH_2); 2.95 and 2.99 (2s, $2(CH_3)_2$); 3.63-4.01 (m, 2CH); 4.53-4.83 (m, CHCO); 6.53-8.53 (15H, NH, arom.);
8c	$C_{31}H_{34}N_8O_2$	67.31 67.62	5.99 6.22	20.16 20.35	220-221, ethanol	DMSO-d_6	2.68-3.08 (m, CH_2); 2.95 and 2.99 (2s, $2(CH_3)_2$); 3.15-3.35 (m, 2CH); 4.50-4.78 (m, CHCO); 5.50-5.85 (s, NH); 6.30-8.63 (14, m, arom.); 10.96-11.50 (m, 2CONH)
9e	$C_{14}H_{11}N_3O_4S$	55.57 55.81	3.90 3.68	14.02 13.95	271 (dec.), ethanol	DMSO-d_6	2.56 and 3.00 (J_{AB} = 17; J_{AX} = 3; J_{BX} = 4, CH_2); 5.31 (t, J = 5, CH); 7.40-9.34 (7H, NH, arom.)
9f	$C_{15}H_{13}N_2O_3S$	56.80 57.13	4.42 4.16	13.08 13.33	200 (dec.), ethanol	DMSO-d_6	2.71 (s, CH_3); 2.56 and 2.94 (J_{AB} = 18; J_{AX} = 4; J_{BX} = 5, CH_2); 5.25 (t, J = 4.5, CH); 6.00-7.05 (m, NH); 7.30-8.33 (5H, m, arom.)

EXPERIMENTAL

^{1}H NMR spectra were recorded on Tesla BS-487C (80MHz) spectrometer with HMDS as internal standard. IR spectra of KBr disks were measured on a UR-20 spectrometer and UV spectra of aqueous solutions ($4 \cdot 10^{-5}$ mol/l) were recorded with a Specord UV-vis spectrophotometer at 20°C. The course of reactions and the purity of materials were monitored by TLC on Silufol and Silufol UV-254 strips.

Diethyl N-(4-Quinolyl)aspartate (3b). A mixture of 4-aminoquinoline (14.4 g, 0.1 mol), diethyl maleate (25.8 g, 0.15 mol), and acetic acid (0.5 ml) was heated for 24 h at 120°C. The reaction mixture was diluted with acetone (100 ml), mixed, and kept for 2 days at 5°C. The precipitate was filtered off, washed with ether and dried to give compound **3b** (17.7 g, 61%).

Diethyl N-(5-Quinolyl)aspartate (3c). A mixture of 5-aminoquinoline (7.2 g, 50 mmol), diethyl maleate (9.5 g, 55 mmol), and acetic acid (0.5 ml) was heated at 120°C for 40 h. The reaction mixture was dissolved in 1:1:1 chloroform–hexane–acetone and passed through a Silpearl 254 silica gel column. The fraction with R_f 0.4 was collected (3.1 g, 20%).

Diethyl N-(2-Methyl-5-quinolyl)aspartate (3d). A mixture of 2-methyl-5-aminoquinoline (7.9 g, 50 mmol), diethyl maleate (9.5 g, 55 mmol), and acetic acid (0.5 ml) was heated for 24 h at 120°C, dissolved in 1:1 hexane–methyl ethyl ketone, and passed through a silica gel column. The fraction with R_f 0.65 was collected (3.65 g, 22%).

N-(3-Quinolyl)aspartic Acid (2a). A mixture of 3-aminoquinoline (5.76 g, 40 mmol), diethyl maleate (7.75 g, 45 mmol), and acetic acid (0.5 ml) was heated for 40 h at 120°C. 10% aqueous sodium hydroxide (40 ml) was added and the mixture was boiled for 25 min. The cold solution was filtered and the filtrate was extracted with chloroform (20 ml × 3). The alkaline solution was acidified with acetic acid to pH 5-6 and kept at 5°C. The precipitate was filtered off, washed with water, and dried to give compound **2a** (3.25 g, 28%).

N-(4-Quinolyl)aspartic Acid (2b). Diethyl ester **3b** (15.8 g, 50 mmol) was boiled in 10% aqueous ethanolic potassium hydroxide solution (50 ml). After cooling, acetic acid was added to a pH of 5-6 and the mixture was kept at 5°C. The precipitated crystals were filtered off, washed with water and ethanol, and dried to give compound **2b** (12 g, 93%). IR spectrum, ν, cm^{-1}: 3320 (NH), 1620 (C=O). UV spectrum, λ_{max}, (log ε): 217 (5.61), 233 (5.33), 329 (5.48), 340 (5.47).

N-(5-Quinolyl)aspartic Acid (2c) was obtained from 5-aminoquinoline (21.6 g, 0.15 mol) analogously to **2a**. Yield 17.4 g (45%).

N-(2-Methyl-5-quinolyl)aspartic Acid (2d) A. was obtained from 5-amino-2-methylquinoline **1d** analogously to **2a**. Yield 9.8 g. **B.** A mixture of amine **1d** (15.8 g, 0.1 mol) , maleic acid (12.7 g, 0.11 mol), and water (100 ml) was boiled for 10 h, then water was removed on a rotary evaporator. The residue was recrystallized from ethanol. Yield 6.3 g (23%). A mixed melting point of samples made by methods A and B gave no depression.

N-(6-Quinolyl)aspartic Acid (2e) A. was prepared from 6-aminoquinoline **1e** (14.4 g, 0.1 mol) analogously to **2a**. Yield 16.4 g (63%).

B. 2e was obtained from **1e** (5.8 g, 40 mmol) analogously to **2d**. Yield 6.4 g (62%).

N-(2-Methyl-6-quinolyl)aspartic Acid (2f) was prepared from 6-amino-2-methylquinoline (**1f**) (15.8 g, 0.1 mol) and diethyl maleate (19 g, 0.11 mol) analogously to **2a**. Yield 20.3 g (74%).

N-(8-Quinolyl)aspartic Acid (2g) was obtained from **1g** (14.4 g, 0.1 mol) analogously to **2a**. Yield 5.8 g (22%).

4-Aminoquinolinium Maleate (4b). A mixture of 4-aminoquinoline (2.9 g, 20 mmol), maleic acid (2.4 g, 21 mmol), and water (50 ml) was boiled for 1 h. After removal of water on a rotary evaporator, the residue was dissolved in ethanol and poured into ether. The precipitate was filtered off, washed with ether, and dried to give **4b** (4.4 g, 83%). IR spectrum, ν, cm^{-1}: 3370, 3200 (NH), 1680 (CO), UV spectrum, λ_{max}, nm (log ε): 215 (5.70), 230 (5.66), 323 (5.43), 333 (5.39).

4-Amino-1-(3-carboxylato-1-oxopropen-2-yl)quinolinium Betaine (5b). A mixture of 4-aminoquinoline (2.79 g, 20 mmol), diethyl maleate (3.6 g, 21 mmol), and water (5 ml) was boiled for 10 h, acetone (100 ml) was added and the mixture was kept at 5°C for 4 h. The precipitate was filtered off, washed with ether, and dried to give **5b** (2.8 g, 83%). IR spectrum, ν, cm^{-1}: 1660 (CO), 1570 (carboxylate ion). UV spectrum, λ_{max}, nm (log ε): 215 (5.73), 230 (5.72), 323 (5.48), 333 (5.45).

Dihydrazides of N-Quinolylaspartic Acids (7b,d,e). A. A diethyl ester **3** (5 mmol) was dissolved in ethanol (20 ml), 85% hydrazine (10 ml) was added, and the mixture was kept for a day at room temperature. The precipitate was filtered off, washed with ether, and dried. Yield 80-90%.

B. A mixture of an aspartic acid **2** (20 mmol), 50% hydrazine (20 ml), and ethanol or dioxane (30 ml) was boiled for 10 h, the liquid fraction was distilled off, and the residue was crystallized from ethanol. Yield 60-75%.

Di-(4-dimethylaminobenzylidenehydrazides) of N-Quinolylaspartic Acids (8b,c). A mixture of dihydrazide **7b** or **7e** (25 mmol), 4-dimethylaminobenzaldehyde (0.78 g, 5.2 mmol), and ethanol (50 ml) was boiled for 10h, then kept at 5°C for a day. The precipitate was filtered off, washed with ethanol, and dried. Yield 70-80%.

5-Carboxymethyl-1-(6-quinolyl)imidazolidin-4-on-2-thione (9e). A mixture of aspartic acid **2e** (5.2 g, 20 mmol), potassium thiocyanate (3.2 g, 30 mmol), and acetic acid (25 ml) was boiled for 15 h, concentrated hydrochloric acid (4 ml) was added, and boiling continued for 2 h. The liquid fraction was removed on a rotary evaporator. The residue was dissolved in water (40 ml), neutralized to pH 7 with sodium carbonate, and kept at 5°C. The precipitate was filtered off, washed with water and dried to give **9e** (2.5 g, 43%). IR spectrum, ν, cm^{-1}: 3160 (NH), 1790, 1720 (CO), 1220, 1170 (imidazolidine ring).

5-Carboxymethyl-1-(2-methyl-6-quinolyl)imidazolidin-4-on-2-thione (9f) was obtained from aspartic acid **2f** (5.48 g, 20 mmol) analogously to **9e**. Yield 5 g (83%). IR spectrum, ν, cm^{-1}: 3460, 3050 (NH), 1760 (CO), 1200, 1180 (imidazolidine ring).

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