ANNELATION TO THE QUINAZOLINE RING. PREPARATION OF SOME SUBSTITUTED 2*H*-IMIDAZO- AND 2,3-DIHYDROPYRIMIDO-[1,2-*c*]QUINAZOLINES

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Preparation of some substituted 2*H*-imidazo[1,2-*c*]quinazolin-3-ones (**2a–2f**) and 2,3-dihydropyrimido[1,2-*c*]quinazolin-4-ones (**3a–3c**) by reaction of corresponding 3*H*-quinazoline-4-thiones (**1a–1d**) with amino acid esters is described. IR, ^{1}H NMR and ^{13}C NMR spectra of the compounds synthesized are presented.

Key words: Imidazo[1,2-*c*]quinazoline; Pyrimido[1,2-*c*]quinazoline.

Tricyclic annelated derivatives of quinazoline exhibit an interesting biological activity. Most of them, such as imidazo[1,2-*c*]- or pyrimido[1,2-*c*]quinazolines show marked adrenomimetic, broncholytic, psychoanaleptic and antidepressant properties[1,2]. The most common way of preparation of the mentioned annelated quinazolines involves reactions of 4-chloro- or 2,4-dichloroquinazolines with aziridine, ethylenediamine or amino alcohol followed by cyclization[3–5].

In the present work we describe preparation of the similar annelated quinazoline derivatives directly from the substituted 2-phenyl-3*H*-quinazoline-4-thiones **1**, which are easily synthesized from the *N*-phenylbenzimidoyl chloride, according to the procedures described in ref.[6].

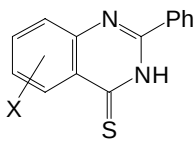
Easy enolization of the thioamidic group in the substituted 3*H*-quinazoline-4-thione **1** enables direct substitution of the thiol group with an amino group of the corresponding amino acid esters.

We have found, that the nucleophilic substitution of the SH group by amino derivatives in boiling solvent (1-butanol, dioxane), under base catalysis (triethylamine, potassium carbonate), takes place very reluctantly. The corresponding esters of substituted *N*-(2-phenyl-3*H*-quinazolin-4-yl)amino acids **4a–4d** were obtained in low yields without preparative value.

The procedure could be improved significantly by carrying it without a solvent. At the temperature of homogeneous melted rection mixture not only a nucleophilic substitution was facilitated but also a thermal cyclization elicited, affording thus directly

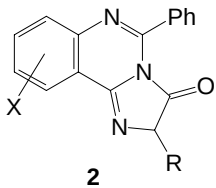
2*H*-imidazo[1,2-*c*]quinazolin-3-ones **2a–2f** and 2,3-dihydropyrimido[1,2-*c*]quinazolin-4-ones **3a–3c** in relatively good yields (Table I).

IR spectra of the prepared compounds show skeletal vibrations as well as the absorption bands at 1 660–1 680 cm^{-1} characteristic of amidic carbonyl group (Table II). ^1H NMR spectra show typical signals of imidazole ring in the region δ = 5.5–5.8 ppm. Triplets of pyrimidine protons were found at δ = 3.5–3.6 ppm and 2.6–2.7 ppm. Multiplets of quinazoline skeleton protons appears at δ = 7.3–8.6 ppm (Table II). The structure of selected final products was supported also with ^{13}C NMR spectra. These spectra exhibit aromatic signals with similar chemical shifts (see Experimental).



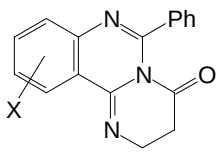
1

1	X
a	H
b	8-CH_3
c	6-Cl
d	6-Br



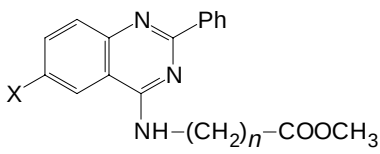
2

2	X	R
a	7-CH_3	H
b	9-Cl	H
c	H	CH_3
d	7-CH_3	CH_3
e	9-Cl	CH_3
f	9-Br	CH_3



3

3	X
a	H
b	8-CH_3
c	10-Br



4

4	X	*n*
a	6-Cl	2
b	6-CH_3	1
c	6-Cl	1
d	6-Br	1

EXPERIMENTAL

IR absorption spectra ($\tilde{\nu}$, cm^{-1}) of synthesized compounds were measured with a Philips PU 9800 FTIR apparatus using the KBr technique. The ^1H NMR spectra (δ, ppm) were measured with a BS 587 A Tesla spectrometer at the working frequency of 80 MHz using hexadeuteriodimethyl sulfoxide as a solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra (δ, ppm) in the same solvent were taken with a Jeol FX-100 spectrometer. The syntheses of starting substituted 3*H*-quinazoline-4-thiones are described elsewhere[7].

Substituted 5-Phenyl-2*H*-imidazo[1,2-*c*]quinazolin-3-ones **2a–2f** and Substituted 6-Phenyl-2,3-dihydropyrimido[1,2-*c*]quinazolin-4-ones **3a–3c**. General Procedure

A homogeneous mixture of the respective substituted 2-phenyl-3*H*-quinazoline-4-thiones **1a–1d** (0.003 mol) and the methyl esters of glycine, α-alanine or β-alanine (0.003 mol) was heated at its

TABLE I
Characteristic data of compounds **2** and **3**

Compound	Formula M.w.	M.p., °C Yield, %	Calculated/Found		
			%C	%H	%N
2a	$C_{17}H_{13}N_3O$	240–242	74.17	4.76	15.26
	275.3	57	73.95	4.62	15.03
2b	$C_{16}H_{10}N_3OCl$	236–238	64.98	3.42	14.21
	295.7	51	65.12	3.13	14.37
2c	$C_{17}H_{13}N_3O$	196–198	74.17	4.76	15.27
	275.3	57	73.87	4.61	14.99
2d	$C_{18}H_{15}N_3O$	214–216	74.72	5.23	14.52
	289.3	58	74.76	5.64	14.68
2e	$C_{17}H_{12}N_3OCl$	222–225	65.92	3.90	13.57
	309.8	61	66.38	3.97	13.70
2f	$C_{17}H_{12}N_3OBr$	162–164	57.65	3.41	11.86
	354.2	53	57.23	3.15	11.57
3a	$C_{17}H_{13}N_3O$	181–183	74.15	4.76	15.27
	275.3	37	74.02	4.55	14.99
3b	$C_{18}H_{15}N_3O$	183–186	74.71	5.23	14.56
	289.3	43	74.59	5.12	14.43
3c	$C_{17}H_{12}N_3OBr$	176–178	57.79	3.73	11.90
	354.2	44	57.65	3.41	11.78

melting temperature (200–220 °C) without solvent on an oil bath for 3–5 min. The obtained melt was dissolved in dioxane (40 ml), boiled with charcoal, filtered and evaporated in vacuum until dry. The residue was recrystallized from ethyl acetate. Characteristic data of compounds **2** and **3** are given in Table I, their IR and NMR spectra in Table II.

9-Chloro-2-methyl-5-phenyl-2H-imidazo[1,2-c]quinazolin-3-one **2e**. ^{13}C NMR spectrum: 18.6 CH_3; 49.8 (C-2 of imidazole ring); 127.8 (1 C), 128.5 (2 C), 130.5 (2 C), 131.7 (1 C), 131.8 (1 C), 132.3 (2 C), 135.3 (1 C), 143.1 (1 C), 152.1 (1 C) (benzene rings); 168.7 (1 C) and 169.0 (1 C) (C=N bonds of pyrimidine ring); 186.7 (C=O).

8-Methyl-6-phenyl-2,3-dihydropyrimido[1,2-c]quinazolin-4-one **3b**. ^{13}C NMR spectrum: 16.4 CH_3; 35.5 (C-2, pyrimidine) and 66.0 (C-3, pyrimidine); 120.9 (1 C), 122.9 (1 C), 126.7 (1 C), 127.3 (1 C), 127.9 (2 C), 130.8 (1 C), 130.9 (1 C), 132.1 (1 C), 134.3 (1 C), 135.0 (1 C), 135.9 (1 C) (benzene rings); 142.5 and 147.8 (C=N bonds of pyrimidine ring); 187.5 (C=O).

Methyl Esters of Substituted *N*-(2-Phenylquinazolin-4-yl)aminoalkanoic Acids **4a–4d**

The respective substituted 2-phenyl-3*H*-quinazolin-4-thione **1a–1d** (0.005 mol), methyl ester of corresponding amino acid (0.005 mol) and K_2CO_3 (0.015 mol; 1.8 g) in dry dioxane (40 ml) was heated at boiling temperature for 3 h and then poured into an ice–water mixture; the product that separated was filtered off and recrystallized from ethanol.

Methyl N-(6-chloro-2-phenylquinazolin-4-yl)aminopropanoate (**4a**). Yield 12%, m.p. 238–240 °C. For $C_{17}H_{12}ClN_3O_2$ (309.1) calculated: 66.01% C, 3.91% H, 16.49% N; found: 65.87% C, 4.21% H, 16.57% N. IR spectrum: 1 728 ν(C=O), 1 610 ν(C=N), 1 217 ν(C–O). ^{1}H NMR spectrum: 7.47–8.49 m, 8 H (arom.); 3.58 s, 3 H (OCH_3); 2.88 t, 2 H (CH_2–N); 2.18 t, 2 H (CH_2–CO).

TABLE II
Spectral properties of compounds **2** and **3**

Compound	IR		^{1}H NMR	
	ν(C=O)	ν(C=N) ν(C=C)	Arom. (m)	Other signals
2a	1 682	1 604	7.23–8.61	5.80 s, 2 H (CH_2); 2.70 s, 3 H (CH_3)
2b	1 664	1 608	7.51–8.52	5.47 s, 2 H (CH_2)
2c	1 684	1 601	7.42–8.61	3.83 q, 1 H (CH); 1.23 d, 3 H (CH_3)
2d	1 680	1 604	7.12–8.36	4.11 q, 1 H (CH); 2.71 s, 3 H (CH_3); 1.38 d, 3 H (CH_3–CH)
2e	1 680	1 608	7.55–8.49	3.84 q, 1 H (CH); 1.19 d, 3 H (CH_3)
2f	1 686	1 603	7.55–8.63	4.06 q, 1 H (CH); 1.21 d, 3 H (CH_3)
3a	1 664	1 603	7.43–8.61	3.60 t, 2 H (CH_2–CO); 2.66 t, 2 H (CH_2–N)
3b	1 660	1 608	7.48–8.36	2.69 s, 3 H (CH_3); 3.48 t, 2 H (CH_2–CO); 2.60 t, 2 H (CH_2–N)
3c	1 664	1 603	7.35–8.75	3.60 t, 2 H (CH_2–CO); 2.66 t, 2 H (CH_2–N)

Methyl N-(8-methyl-2-phenylquinazolin-4-yl)aminoacetate (**4b**). Yield 17%, m.p. 247–249 °C. For $C_{17}H_{15}N_3O$ (203.3) calculated: 69.61% C, 5.15% H, 14.33% N; found: 69.54% C, 5.13% H, 14.06% N. IR spectrum: 1 719 ν(C=O), 1 604 ν(C=N), 1 217 ν(C–O). ^{1}H NMR spectrum: 7.31–8.47 m, 8 H (arom.); 13.74 brs, 1 H (NH); 4.20 s, 2 H (CH_2); 3.86 s, 3 H (OCH_3); 2.62 s, 3 H (CH_3).

Methyl N-(6-chloro-2-phenylquinazolin-4-yl)aminoacetate (**4c**). Yield 19%, m.p. 236–238 °C. For $C_{17}H_{14}ClN_3O_2$ (327.1) calculated: 62.39% C, 4.31% H, 12.84% N; found: 62.44% C, 4.25% H, 12.59% N. IR spectrum: 1 743 ν(C=O), 1 610 ν(C=N), 1 218 ν(C–O). ^{1}H NMR spectrum: 13.87 brs, 1 H (NH); 7.36–8.36 m, 8 H (arom.); 4.08 s, 2 H (CH_2); 3.51 s, 3 H (OCH_3).

Methyl N-(6-bromo-2-phenylquinazolin-4-yl)aminoacetate (**4d**). Yield 11%, m.p. 242–247 °C. For $C_{17}H_{13}BrN_3O$ (370.0) calculated: 55.13% C, 3.54% H, 11.35% N; found: 55.28% C, 3.29% H, 11.42% N. IR spectrum: 1 720 ν(C=O), 1 603 ν(C=N), 1 211 ν(C–O). ^{1}H NMR spectrum: 13.98 brs, 1 H (NH); 7.55–8.64 m, 8 H (arom.); 4.33 s, 2 H (CH_2); 3.54 s, 3 H (OCH_3).

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