Use of amidinoyl isothiocyanates in the synthesis of condensed heterocycles Preparation of 2,3-dihydroimidazo- and 2,3,4-trihydropyrimido-[1,2-*c*]quinazolines

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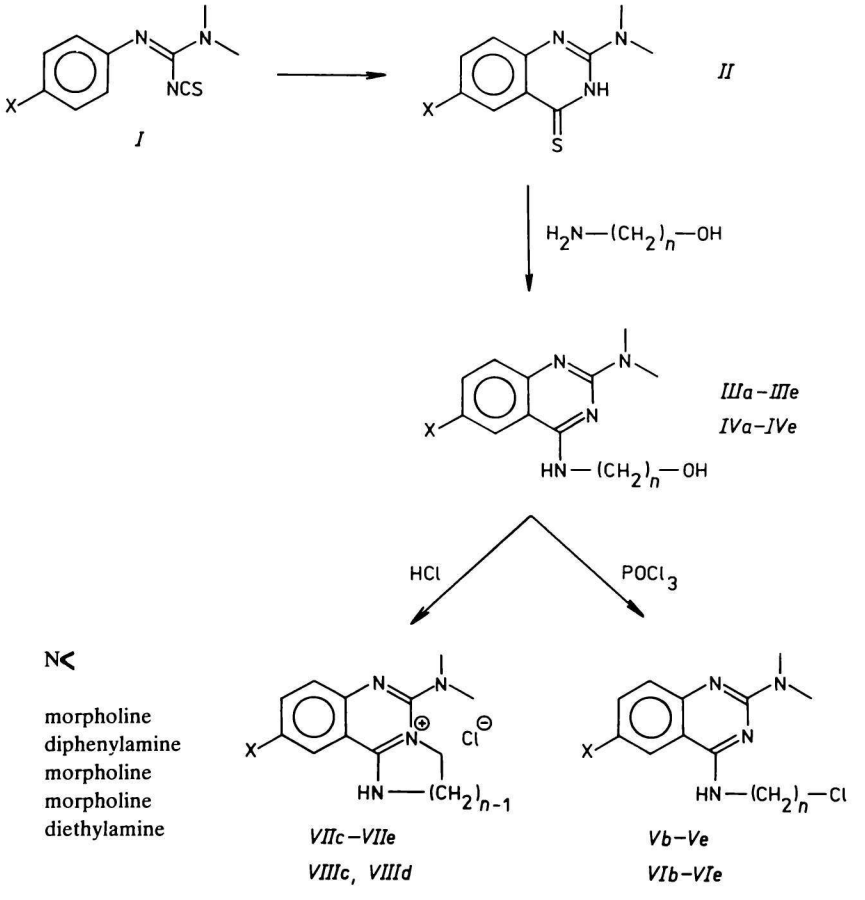
Reactions of substituted 4-(2-hydroxyethylamino)- and 4-(3-hydroxypropylamino)quinazolines with phosphoric oxychloride or with concentrated hydrochloric acid under heating are described. New reaction intermediates and final imidazo- and pyrimido[1,2-*c*]quinazolines were characterized by infrared and ultraviolet absorption spectra.

Описаны реакции замещенных 4-(2-гидроксиэтиламино)- и 4-(3-гидроксипропиламино)хиназолинов с оксохлоридом фосфора или с концентрированной соляной кислотой при нагревании. Новые промежуточные соединения и конечные имидазо- и пиримидо[1,2-*c*]хиназолины были охарактеризованы своими ИК и УФ-адсорбционными спектрами.

Condensed quinazolines containing an imidazole or pyrimidine skeleton on the side *c* were not studied extensively before 1970 [1—5]. New possibilities of their synthesis and applications were investigated only after discovery of their interesting pharmacological properties [4, 5].

The most common way of the preparation of condensed quinazolines involves reactions of 4-chloroquinazolines or 2,4-dichloroquinazolines with aziridine [6—8], ethylenediamine [3], 2-amino-1-ethanol or 3-amino-1-propanol [1, 8—10] followed by cyclization in the presence of a suitable condensation agent.

In order to overcome the tedious preparation of 4-chloroquinazoline we describe in this paper the preparation of the starting substituted quinazoline-4-amino alcohols in reactions of easily available quinazoline-4-thiones with 2-amino--1-ethanol or 3-amino-1-propanol. Quinazoline-4-thiones substituted in the position 2 with a *sec*-amino group (compounds *II*) were obtained almost in quantitative yields on heating of the corresponding amidinoyl isothiocyanates (*I*) in benzene (Scheme 1).



	X	N<
a	H	morpholine
b	H	diphenylamine
c	Cl	morpholine
d	Br	morpholine
e	Br	diethylamine

$n = 2,3$

Scheme 1

Survey of all reactions carried out

Easy enolization of the thioamidic group in *I*, in contrast to their oxy analogues, quinazolines, enables direct substitution of the SH group with the amino group of the corresponding amino alcohol. New 4-(2-hydroxyethylamino)quinazolines (*IIIa—IIIe*) and 4-(3-hydroxypropylamino)quinazolines (*IVa—IVe*) prepared in this way are listed in Table 1. Their infrared spectra contain besides the characteristic absorption bands corresponding to the vibrations of the C=C and C=N bonds of the quinazoline skeleton ($\tilde{\nu} = 1570$ cm^{-1} and 1610 cm^{-1}) a complex absorption band with sharp maxima at $\tilde{\nu} = 3100$ cm^{-1} and 3300 cm^{-1} corresponding to the vibrations of the OH and NH groups.

Table 1

Properties and characteristic absorption bands in the infrared spectra of the prepared 4-(2-hydroxyethylamino)quinazolines *IIIa—IIIe* and 4-(3-hydroxypropylamino)quinazolines *IVa—IVe*

Compound	X	N< * n	Formula	M_r	w_i(calc.)/% w_i(found)/%			M.p./°C Yield/%	$\tilde{\nu}_i$/cm^{-1}			
					C	H	N		C=C	C=N	CH_{ali}	(NH, OH)
IIIa	H	Mo 2	$C_{14}H_{18}N_4O_2$	274.3	61.30 61.24	6.61 6.56	20.42 20.53	196—200 64	1570	1620	2850 2920	3160 3310
IVa	H	Mo 3	$C_{15}H_{20}N_4O$	288.3	62.74 62.38	6.99 7.13	19.43 19.24	173—178 63	1575	1610	2840 2910	3160 3310
IIIb	H	DP 2	$C_{22}H_{20}N_4O$	356.4	74.14 74.28	5.67 5.58	15.72 15.61	219—220 65	1570	1615	— —	3140 3270
IVb	H	DP 3	$C_{23}H_{22}N_4O$	370.4	74.57 74.63	5.99 5.84	15.12 15.28	188—190 80	1575	1615	— —	3140 3285
IIIc	Cl	Mo 2	$C_{14}H_{17}N_4O_2Cl$	308.7	54.46 54.61	5.55 5.64	18.14 18.20	198—202 71	1575	1615	2825 2900	3140 3300
IVc	Cl	Mo 3	$C_{15}H_{19}N_4O_2Cl$	322.7	55.89 55.74	5.93 6.05	17.36 17.28	210—214 73	1570	1615	2800 2920	3160 3300
IIId	Br	Mo 2	$C_{14}H_{17}N_4O_2Br$	353.2	47.61 47.76	4.85 4.94	15.86 15.93	209—211 68	1565	1610	2828 2900	3160 3325
IVd	Br	Mo 3	$C_{15}H_{19}N_4O_2Br$	367.2	49.06 48.91	5.21 5.32	15.26 15.39	203—206 70	1570	1610	2800 2900	3120 3305
IIIe	Br	DE 2	$C_{14}H_{19}N_4OBr$	339.2	49.57 49.69	5.64 5.52	16.52 16.84	158—162 66	1565	1610	2840 2890	3120 3310
IVe	Br	DE 3	$C_{15}H_{21}N_4OBr$	353.2	51.00 51.17	5.99 5.84	15.86 15.97	198—202 63	1570	1610	2830 2900	3140 3320

* Mo — morpholine, DP — diphenylamine, DE — diethylamine.

Cyclization of such amino alcohols can be accomplished essentially by two procedures. In the first one, amino alcohol is reacted with thionyl chloride or phosphoric oxychloride to give the corresponding chloride which is either isolated or directly subjected to thermal cyclization [8—10].

The compounds identified as the corresponding 4-(2-chloroethylamino)quinazolines *Vb—Ve* and 4-(3-chloropropylamino)quinazolines *VIb—VIe* (Table 2) were obtained after heating of the selected 4-(2-hydroxyethylamino)quinazolines *IIIb—IIIe* and 4-(3-hydroxypropylamino)quinazolines *IVb—IVe* in the excess of $POCl_3$. It can be assumed that the low boiling temperature of $POCl_3$ is insufficient to overcome the unfavourable steric relations caused by the bulky *sec*-amino group on the neighbouring atom. The cyclization does not take place even under prolonged heating and the reaction is terminated at the stage of a stable intermediate easy to isolate. From the mother liquors obtained after isolation of the chlorides *Vb—Ve* and *VIb—VIe*, unreacted amino alcohols *IIIb—IIIe* and *IVb—IVe* were recovered in 30—35 % yields when referred to the starting amounts. However, the amino alcohols could also originate in hydrolysis of chlorides during neutralization of the reaction mixtures as well as in the hydrolysis of phosphoric acid esters, the formation of which cannot be excluded in the above reactions.

An alternative cyclization of amino alcohols *III* and *IV* consists in their long-term heating in concentrated hydrochloric acid. The mechanism of this cyclization has not been elucidated yet, but a proposal was made that it proceeded through 4-aziriniumquinazoline chloride as an intermediate which thermally isomerizes into the corresponding imidazolium salt [1].

The insoluble crystalline compounds formed from the selected quinazoline-4-amino alcohols *IIIc—IIIe* and *IVc, IVd* during a 5 h heating in concentrated hydrochloric acid are listed in Table 3. Based on the results of elemental analysis, infrared and ultraviolet spectra, and a comparison with the literature data [1, 10] the structure of these compounds was established as 1,2,3-trihydroimidazo[1,2-*c*]quinazolinium chlorides (*VIIc—VIIe*) and 1,2,3,4-tetrahydropyrimido[1,2-*c*]quinazolinium chlorides (*VIIIc, VIIId*). Infrared spectra of the compounds contain besides the absorption bands characteristic of substituted quinazolines, $\tilde{\nu}$(C=N) at 1620 cm^{-1}, an intense absorption band at $\tilde{\nu} = 1670$ cm^{-1} which can be ascribed to vibrations of the iminium group $-\overset{|}{C}=\overset{\oplus}{\underset{|}{N}}-$ [11, 12]. The absorption band at $\tilde{\nu} = 3100$ cm^{-1} corresponds to vibrations of the NH group. In ultraviolet spectral region of $\lambda = 230$—330 nm the compounds exhibit four absorption bands which do not overlap the visible spectral region. The least intense band lies at the longest wavelength.

The quinazolinium cation formed in the above reactions can exist in two mesomeric forms VII_A or $VIII_A$ and VII_B or $VIII_B$, respectively (Scheme 2). The

Table 2

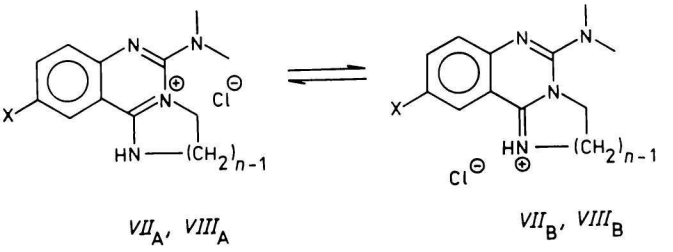
Properties and characteristic absorption bands in the infrared spectra of the prepared 4-(2-chloroethylamino)quinazolines *Vb*—*Ve* and 4-(3-chloropropylamino)quinazolines *VIb*—*VIe*

Compound	X	N< *n*	Formula	M_r	w_i(calc.)/% w_i(found)/%			M.p./°C Yield/%	$\tilde{\nu}_i$/cm^{-1}			
					C	H	N		C=C	C=N	CH_{aliph}	NH
Vb	H	DP 2	$C_{22}H_{19}N_4Cl$	374.8	70.49 70.56	5.11 5.24	14.95 14.81	136—138 56	1570	1620	—	3200
VIb	H	DP 3	$C_{23}H_{21}N_4Cl$	388.9	71.03 71.17	5.44 5.51	14.41 14.33	130—134 38	1565	1620	—	3210
Vc	Cl	Mo 2	$C_{14}H_{16}N_6OCl$	327.2	51.39 51.47	4.93 4.97	17.12 17.24	146—149 57	1575	1620	2795	3370
VIc	Cl	Mo 3	$C_{15}H_{18}N_4OCl_2$	341.2	52.80 52.65	5.32 5.41	16.42 16.31	132—139 52	1570	1620	2800	3360
Vd	Br	Mo 2	$C_{14}H_{16}N_4OClBr$	371.6	45.24 45.36	4.34 4.42	15.07 14.93	150—154 40	1570	1617	2790	3365
VId	Br	Mo 3	$C_{15}H_{18}N_4OClBr$	385.6	46.71 46.87	4.70 4.63	14.53 14.61	136—138 34	1570	1615	2840	3380
Ve	Br	DE 2	$C_{14}H_{18}N_4ClBr$	357.6	47.01 47.20	5.07 5.17	15.66 15.51	150—155 41	1570	1615	2870	3340
VIe	Br	DE 3	$C_{15}H_{20}N_4ClBr$	371.7	48.47 48.32	5.42 5.53	15.07 15.16	154—158 37	1570	1610	2840	3320

Table 3

Yields, physical constants, and spectral characteristics of substituted 1,2,3-trihydroimidazo- and 1,2,3,4-tetrahydropyrimido[1,2-*c*]quinazolinium chlorides *VIIc—VIIe, VIIIc, VIIId*

Compound	X	N_{n-1}	Formula	M_r	w_i(calc.)/% w_i(found)/%			M.p./°C Yield/%	$\tilde{\nu}_i$/cm^{-1}		UV			
					C	H	N		C=N $C=\overset{\oplus}{N}-$	CH NH	λ_{max}/nm			
											log (ε/(dm^3 mol^{-1} cm^{-1}))			
VIIc	Cl	Mo	$C_{14}H_{16}N_4Cl_2O$	327.2	51.39	4.93	17.12	305—308	1615	2850, 2960	233	250	280	332
		1			51.43	4.86	17.14	40	1675	3140	3.305	3.129	3.098	2.383
VIIIc	Cl	Mo	$C_{15}H_{18}N_4Cl_2O$	341.2	52.80	5.32	16.42	288—293	1610	2840, 2950	231	249	280	331
		2			52.76	5.36	16.49	40	1675	3120	3.465	3.292	3.276	2.568
VIId	Br	Mo	$C_{14}H_{16}N_4ClBrO$	371.6	45.24	4.34	15.07	325—326	1640	2760, 2850	233	251	280	330
		1			45.38	4.27	15.19	38	1700	3100	3.523	3.338	3.257	2.513
VIIId	Br	Mo	$C_{15}H_{18}N_4BrClO$	385.6	46.71	4.70	14.53	297—301	1615	2860, 2960	233	252	283	331
		2			46.74	4.58	14.53	70	1670	3120	3.540	3.346	3.326	2.680
VIIe	Br	DE	$C_{14}H_{18}N_4ClBr$	357.6	47.01	5.07	15.68	264—267	1605	2920, 2980	234	251	282	331
		1			47.20	5.14	15.63	36	1680	3120	3.618	3.566	3.278	2.657



Scheme 2

Possible tautomeric structures of trihydroimidazo- and tetrahydropyrimido-[1,2-*c*]quinazolinium cations

absorption band in the infrared spectra of the compounds at $\tilde{\nu} = 3100\ \mathrm{cm}^{-1}$ indicates that we deal here with the structures VII_A or $VIII_A$. The absorption band corresponding to the vibrations of the $=\overset{\oplus}{\mathrm{N}}\text{—H}$ group, present in the structures VII_B or $VIII_B$ should have appeared in the range of $\tilde{\nu} = 2500\text{—}2000\ \mathrm{cm}^{-1}$.

Attempts to cyclize the compounds *IIIb* and *IVb* were unsuccessful, obviously due to the steric hindrance by the bulky diphenylamino group. The structure of unsubstituted 1,2,3-trihydroimidazo[1,2-*c*]quinazolinium chloride [1] was also established by spectral methods. The low solubility of the compounds in water and diluted hydrochloric acid can be accounted for by low capability of solvation of the nitrogen bridge as a consequence of the steric barrier caused by the voluminous *sec*-amino group.

Other compounds which could be isolated from the reaction mother liquors in 20—30 % yields were identified as hydrochlorides of the starting amino alcohols *IIIc—IIIe* and *IVc, IVd.* We did not succeed in preparation of free bases from compounds *VII* and *VIII* using either potassium carbonate or sodium hydroxide for neutralization. Similar phenomenon was also observed in the case of unsubstituted 1,2,3-trihydroimidazo[1,2-*c*]quinazoline [1] in which during neutralization under heating the imidazole undergoes ring opening.

Experimental

Starting amidinoyl isothiocyanates *I* and the corresponding 3*H*-quinazoline-4-thiones were prepared by procedures described in [13] and [14].

Infrared absorption spectra of the prepared compounds were recorded with a double-beam IR-71 spectrophotometer (Zeiss, Jena) using KBr technique.

Electronic absorption spectra of the final products in the visible and ultraviolet spectral region were measured with a Specord UV VIS spectrophotometer (Zeiss, Jena). Spectra in

the region of $\lambda = 200$—800 nm were measured in 10 mm quartz cuvettes in methanol at compound concentration 3—6 × 10^{-5} mol dm^{-3}.

Substituted 4-(2-hydroxyethylamino)quinazolines IIIa—IIIe and 4-(3-hydroxypropylamino)quinazolines IVa—IVe

The corresponding 3*H*-quinazoline-4-thione (5 mmol) was heated with 2-amino-1-ethanol or 3-amino-1-propanol (1.5 cm^3) at 150 °C for 2 h. After the reaction was completed, as indicated by ceasing hydrogen sulfide development, the mixture was cooled to 60 °C, ethanol (3—5 cm^3) was added and the separated crystals collected by filtration. After purification with activated charcoal the product was crystallized from 1-butanol. The yields and physical constants of the prepared compounds are presented in Table 1.

Preparation of 4-(2-chloroethylamino)quinazolines Vb—Ve and 4-(3-chloropropylamino)quinazolines VIb—VIe

The corresponding amino alcohol *IIIb—IIIe* or *IVb—IVe* (5 mmol) was dissolved in $POCl_3$ (15 cm^3) and refluxed for 1 h. $POCl_3$ was then removed by distillation and the residue mixed with dry benzene (10 cm^3) which was also distilled off. Cold water (20 cm^3) was added and the pH of the mixture was adjusted to 8—10 with 25 % solution of NaOH. After the appearance of the solid product the mixture was stirred for 20 min and heated shortly on a water bath. Provided pH of the mixture remained in the above range, the product was sucked off, treated with charcoal and recrystallized from ethanol. The yields and physical constants of the prepared compounds are given in Table 2.

Preparation of 1,2,3-trihydroimidazo[1,2-c]quinazolinium chlorides VIIc—VIIe and 1,2,3,4-tetrahydropyrimido[1,2-c]-quinazolinium chlorides VIIIc, VIIId

The corresponding amino alcohol *IIIc—IIIe* or *IVc, IVd* (5 mmol) was refluxed in concentrated hydrochloric acid (5 cm^3) at 120 °C for 5 h. The mixture was diluted with cold water (15 cm^3), adjusted to pH = 8—9 with 25 % solution of NaOH and heated shortly on a water bath. Keeping pH still in the above interval, the precipitate was sucked off, treated with charcoal and crystallized from 1-butanol. The yields and physical constants of the prepared products are shown in Table 3.

References

1. Sherill, M. L., Ordelt, E., Duckworth, S., and Budelstein, Z., *J. Org. Chem. 19,* 699 (1954).
2. Grout, R. J. and Partritge, M. W., *J. Chem. Soc. 1960,* 3551.
3. Kolodynska, Z. and Biniecki, S., *Acta Pol. Pharm. 21,* 225 (1964).
4. Fryer, R. J., Earley, I. V., and Sternbach, L. N., *J. Org. Chem. 32,* 3798 (1967).
5. Schindler, O., *U.S.* 3309369; *Chem. Abstr. 67,* 73617 (1967).
6. *Ger. Offen.* 1946188; *Chem. Abstr. 72,* 132774 (1970).
7. Hardtman, G. E. and Ott, H., *J. Org. Chem. 39,* 3599 (1974).
8. Claudi, F., Franchetti, P., Grifantini, M., and Martelli, S., *J. Org. Chem. 39,* 3508 (1974).
9. Wagner, G. and Bunk, E., *Pharmazie 34,* 211 (1979).
10. Yoshikawa, T. and Shitago, K., *J. Pharm. Soc. Jap. 94,* 417 (1974); *Chem. Abstr. 81,* 120561 (1974).
11. Armarego, W., Katritzky, A. R., and Ridgewell, B. I., *Spectrochim. Acta 20,* 593 (1964).
12. Bazzignana, P., Cogrossi, C., Gandino, M., and Merli, P., *Spectrochim. Acta 21,* 605 (1965).
13. Stankovský, Š. and Martvoň, A., *Chem. Zvesti 34,* 253 (1980).
14. Filip, A., *Diploma Thesis.* Slovak Technical University, Bratislava, 1983.

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