AMIDINOYL ISOTHIOCYANATES IN THE SYNTHESIS OF CONDENSED QUINAZOLINES. PREPARATION OF *s*-TRIAZOLO[4,3-*c*]QUINAZOLINES

Štefan STANKOVSKÝ and Mária SOKYROVÁ

Department of Organic Chemistry,
Slovak Institute of Technology, 812 37 Bratislava

Received October 7th, 1983

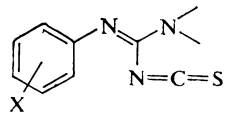
The *s*-triazolo[4,3-*c*]quinazolines were obtained from 4-hydrazinoquinazolines by condensation with ethyl orthoformate. 4-Hydrazinoquinazolines were prepared by hydrazinolysis of correspoding quinazoline-4-thiones which in turn were obtained by isomerization of amidinoyl isothiocyanates. The infrared and ^{1}H NMR spectra of the final products are interpreted.

Quinazolines with a fused triazole ring of type *a* or *b* have been known for more than 50 years; those of the six possible types of *s*-triazoloquinazolines, the [1,5-*a*] and [4,3-*c*] were only recently synthesized. The latter was obtained[1] by reaction of 4-chloroquinazoline with 1-phenyltetrazole, which afforded 4-(3-tetrazolyl)quinazoline, the thermal decomposition of which yielded 3-phenyl-*s*-triazolo[4,3-*c*]quinazoline. The same compound was obtained by cyclization of 4-(benzoyl)hydrazinoquinazoline with phosphorus oxychloride[2], or by oxidative cyclization of the corresponding phenylhydrazone with ferric chloride[3]. A general method for the synthesis of condensed heterocycles, where the heterocycle is attached to $C_{(3)}$—$C_{(4)}$ of *s*-triazole is the reaction of 2-heteroarylhydrazine with aliphatic acids or their derivatives with orthoesters[4]. Thus, orthoesters give with 4-hydrazinoquinazolines substituted in position 2 by methyl, ethyl, phenyl, 2-furyl, or 4-pyridyl groups the remaining *s*-triazolo[4,3-*c*]quinazolines already reported[5–7].

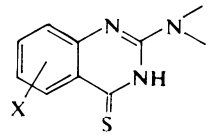
This paper concerns the preparation of title compounds substituted in position 5 by a sec-amino group; these compounds might display, by analogy with other condensed *s*-triazoles, a biological activity[7].

The easily available amidinoyl isothiocyanates *I*, cyclizing spontaneously to 3*H*-quinazoline-4-thiones *II* were employed for construction of the quinazoline backbone. 4-Hydrazinoquinazolines *IIIa*–*IIIh* were obtained by a hydrazinolysis of the corresponding thiones, which, in contrast to their oxygen-containing analogues – quinazolones, underwent this reaction. Yields of 4-hydrazinoquinazolines were not high (Table I), since products of substitution of the sec-amino group with hydrazine were parallely formed; this feature was observed with all experiments after longer-lasting heating. The triazole ring was obtained by condensation of 4-hydrazino-

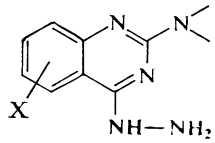
quinazolines prepared in this way with ethyl orthoformate. As known, condensed *s*-triazoles easily undergo isomerization in the presence of acids, bases, or by heat following the mechanism analogous to that of Dimroth rearrangement[6]. To avoid this isomerization a small amount of anhydrous potassium carbonate was added



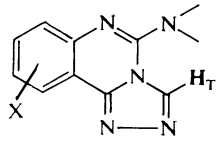
I



II



III



IV

TABLE I

4-Hydrazinoquinazolines *IIIa*—*IIIh*

Compound	X N< [a]	Formula (M_r)	Calculated/Found			M.p., °C (yield, %)
			% C	% H	% N	
IIIa	H	$C_{12}H_{15}N_5O$	58·74	6·17	28·56	239—240
	Mo	(245·1)	58·80	6·35	28·30	(65)
IIIb	H	$C_{12}H_{17}N_5$	62·30	7·41	30·29	169—170
	DE	(231·1)	62·17	7·53	30·11	(62)
IIIc	H	$C_{20}H_{17}N_5$	73·36	5·24	21·40	208—210
	DP	(327·1)	73·10	5·36	21·19	(66)
IIId	H	$C_{13}H_{18}N_6$	60·43	7·03	32·55	198—200
	MPA	(258·2)	60·23	7·15	32·67	(65)
IIIe	6-Br	$C_{12}H_{14}BrN_5O$	44·44	4·35	21·61	211—212
	Mo	(324·0)	44·35	4·50	21·48	(74)
IIIf	6-Br	$C_{13}H_{16}BrN_5$	48·44	5·01	21·74	204—206
	Pi	(322·0)	48·53	5·19	21·52	(67)
IIIg	6-Cl	$C_{12}H_{14}ClN_5O$	51·50	5·05	25·04	200—202
	Mo	(279·6)	51·32	5·20	25·19	(74)
IIIh	5-CH_3	$C_{13}H_{17}N_5O$	60·20	6·61	27·02	193—196
	Mo	(259·1)	60·07	6·50	28·18	(65)

[a] Mo morpholine, DE diethylamine, DP diphenylamine, MPA N-methylpiperazine, Pi piperidine.

to the mixture to neutralize the possible traces of acid in ethyl orthoformate. Yields and melting points of *s*-triazolo[4,3-*c*]quinazolines are listed in Table II. Their IR spectra (Table III) show a very intense absorption band at 1 610 cm^{-1} associated with ν(C=N) vibrations. The high intensity of this band indicates that it cummulates the C=N vibrations of both the triazole and pyrimidine rings. The ^{1}H NMR spectra (Table IV) reveal an easily distinguishable proton singlet of the triazole ring at δ 8·7 ppm shifted behind the aromatic ring proton-region. The presence of an *s*-triazolo-[1,5-*c*] derivative, which could originate through a possible isomerization, was not observed.

EXPERIMENTAL

The starting amidinoyl isothiocyanates were prepared according to[8], substituted 3*H*-quinazoline-4-thiones *II* were synthesized by heating compound *I* in benzene or toluene (*IIc*) and crystallization from ethanol. The IR spectra of chloroform solutions were recorded with a UR-20 (Zeiss,

TABLE II

s-Triazolo[4,3-*c*]quinazolines *IVa*—*IVh*

Compound	X N< [a]	Formula (M_r)	Calculated/Found			M.p., °C (yield, %)
			% C	% H	% N	
IVa	H	$C_{13}H_{13}N_5O$	61·15	5·14	27·45	175—177
	Mo	(255·1)	61·23	5·30	27·30	(68)
IVb	H	$C_{13}H_{15}N_5$	64·70	6·27	29·04	113—115
	DE	(241·1)	64·51	6·11	29·30	(62)
IVc	H	$C_{21}H_{15}N_5$	74·75	4·49	20·77	185—187
	DP	(337·1)	74·58	4·51	20·97	(69)
IVd	H	$C_{14}H_{16}N_6$	62·65	6·02	31·33	190—192
	MPA	(268·1)	62·38	6·23	31·48	(58)
IVe	9-Br	$C_{13}H_{12}BrN_5O$	46·71	3·62	20·96	226—227
	Mo	(334·0)	46·60	3·51	20·73	(61)
IVf	9-Br	$C_{13}H_{13}BrN_6$	46·84	3·93	25·23	220—221
	Pi	(333·0)	46·51	3·70	25·17	(59)
IVg	9-Cl	$C_{13}H_{12}ClN_5O$	53·88	4·18	24·18	203—205
	Mo	(289·5)	53·71	4·11	24·30	(59)
IVh	10-CH_3	$C_{14}H_{15}N_5O$	62·42	5·62	26·02	234—246
	Mo	(269·1)	62·51	5·40	26·19	(55)

[a] For abbreviations see Table I.

Jena) spectrophotometer in the 1 600—700 cm^{-1} region in a 0·26 mm-NaCl cell. The ^1H NMR spectra of C^2HCl_3 solutions were measured with a Tesla BS 487 C apparatus operating at 80 MHz, tetramethylsilane was the internal reference.

Substituted 4-Hydrazinoquinazolines *IIIa—IIIh*

A solution of the respective quinazoline-4-thione (10 mmol) and hydrazine hydrate (80%, 5 ml) in 99%-ethanol (100 ml) was refluxed till the evolution of hydrogen sulfide ceased (5—10 h). The substituted quinazoline was filtered off after cooling, the filtrate was concentrated to its 1/5th and the precipitated second crop was filtered off. The combined product was crystallized from ethanol with an addition of charcoal.

Substituted *s*-Triazolo[4,3-*c*]quinazolines *IVa—IVh*

4-Hydrazinoquinazoline (2 mmol) *III*, redistilled ethyl orthoformate (10 ml) and anhydrous potassium carbonate (0·5 g) were refluxed for 3·5 h. The excess of potassium carbonate was filtered

TABLE III
Characteristic IR-absorption bands (cm^{-1}) of *s*-triazolo[4,3-*c*]quinazolines *IVa—IVh*

Compound	X N< [a]	ν(C=C)	ν(C=N)	νCH_{aliph}	νCH_{arom}
IVa	H	1 527	1 613	2 845	2 982
	Mo	1 561		2 882	
				2 917	
IVb	H	1 560	1 611	2 860	2 977
	DE	1 576		2 920	
IVc	H	1 560	1 613	—	2 980
	DP	1 587			
IVd	H	1 525	1 610	2 789	2 981
	MPA	1 540		2 840	
				2 927	
IVe	9-Br	1 528	1 614	2 850	2 987
	Mo	1 555		2 910	
IVf	9-Br	1 527	1 611	2 844	2 981
	Pi	1 561		2 930	
IVg	9-Cl	1 515	1 600	2 841	2 955
	Mo			2 881	
				2 905	
IVh	10-CH_3	1 526	1 610	2 845	2 950
	Mo			2 883	

[a] For abbreviations see Table I.

TABLE IV

^{1}H NMR signals (δ, ppm) of *s*-triazolo[4,3-*c*]quinazolines *IVa*—*IVh*

Compound	X / N< [a]	H_T	H_{Ar}	H_S
IVa	H Mo	8·75 s	8·45—7·69	3·90 m; 3·60 m
IVb	H DE	8·75 s	8·52—7·35	3·57 m; 1·35 m
IVc [b]	H DF	8·60 s	8·50—7·30	—
IVd	H MPA	8·75 s	8·40—7·35	3·65 m; 2·65 m
IVe	9-Br Mo	8·77 s	8·65—7·50	3·95 m; 3·60 m
IVf	9-Br Pi	8·72 s	8·65—7·57	3·50 m; 1·77 m
IVg	9-Cl Mo	8·72 s	8·45—7·60	3·90 m; 3·55 m
IVh [c]	10-CH_3 Mo	8·80 s	8·40—7·60	3·95 m; 3·70 m

[a] For abbreviations see Table I; [b] 2·40 s, N—CH_3; [c] 3·15 s, N—CH_3.

off from the hot solution, the residue was evaporated and crystallized from benzene with an addition of charcoal.

REFERENCES

1. Huisgen R., Sturm H. J., Seidel M.: Chem. Ber. *94*, 1955 (1961).
2. Sidhu G. S., Rao N.: Naturwissenschaften *50*, 732 (1963).
3. Naqui S., Srinivasan V. R.: J. Sci. Ind. Research *21* B, 456 (1962).
4. Potts K. T.: Chem. Rev. *61*, 87 (1961).
5. Postovski I. Ya., Vereschagina N. N., Mertsalov S. L.: Khim. Geterotsikl. Soedin. *1966*, 130.
6. Potts K. T., Brugel E. G.: J. Org. Chem. *35*, 3448 (1970).
7. Chaurasia M. R., Sharma S. K.: Heterocycles *14*, 1761 (1980).
8. Stankovský Š., Martvoň A.: Chem. Zvesti *34*, 253 (1980).

Translated by Z. Votický.