Synthesis and Reactivity of 1,2,4-Triazolo[1,5-*c*]quinazolines

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The preparation of 1,2,4-triazolo[1,5-*c*]quinazolines **4a-d, 5, 8a-d** by cyclocondensation of **1a-c** with carboxylic acids and carboxylic anhydrides, respectively, is described. By different pathways, the 5-thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines **4a-d** react with hydrazine hydrate or amines with the formation of 5-substituted 1,2,4-triazolo[1,5-*c*]quinazolines **9** and **10a-d**. Cyclocondensation of **9** with carboxylic acids, carboxylic anhydrides, and nitrous acid, respectively, leads to the new anellated heterocycles bis-1,2,4-triazolo[4,3-*a*:1,5-*c*]quinazoline **13** and tetrazolo [1,5-*a*]-1,2,4-triazolo[1,5-*c*]quinazoline (**14**).

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Introduction.

Quinazolines as well as their anellated derivatives are known to form a pharmacologically interesting class of compounds [1-4]. Liu *et al.* [5] synthesized 1,2,4-triazolo[5,1-*b*]-quinazolines with antihypertonic activity. Some 1,2,4-triazolo[1,5-*c*]quinazolines show remarkable antiviral activity [6]. Kathawala *et al.* [7-9] described 1,2,4-triazolo-[1,5-*c*]quinazolines with antiflammatory and antihypertonic properties. Only a few synthetic methods of 1,2,4-triazolo-[1,5-*c*]quinazolines can be found in the literature. Potts and Brugel [10] obtained triazolo[1,5-*c*]quinazolines by treatment of 3-substituted 4-hydrazinoquinazolines with orthoesters in the presence of potassium carbonate. Francis *et al.* obtained 5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines by cyclization of 2-(1,2,4-triazol-3-yl)benzamides with sodium hypobromite and lead tetraacetate, respectively [11]. Stankovsky *et al.* [12] used an oxidative cyclization of the corresponding 4-quinazolinecarbaldehyde hydrazones for the preparation of these systems. The benzoxazine derivatives can undergo an interesting ring transformation to substituted 1,2,4-triazolo[1,5-*c*]quinazolines by treatment with amino-guanidines [13] and thiosemicarbazides [14], respectively.

Up to the present, no methods have been described for the synthesis of 1,2,4-triazolo[1,5-*c*]quinazolines *via* direct ring anellation on the quinazoline skeleton with amino substituents in position 3 and imino groups in position 4. Therefore the objective of our work was focused on a study of reaction conditions, which are applicable for the formation of these ring systems by reaction of 3-amino-4-imino-2-thioxo-1,2,3,4-tetrahydroquinazoline (**1a**), and its 2-selenoxo **1b** or the 2-oxo analogue **1c** with carboxylic acids, their orthoesters and anhydrides, respectively.

Results and Discussion.

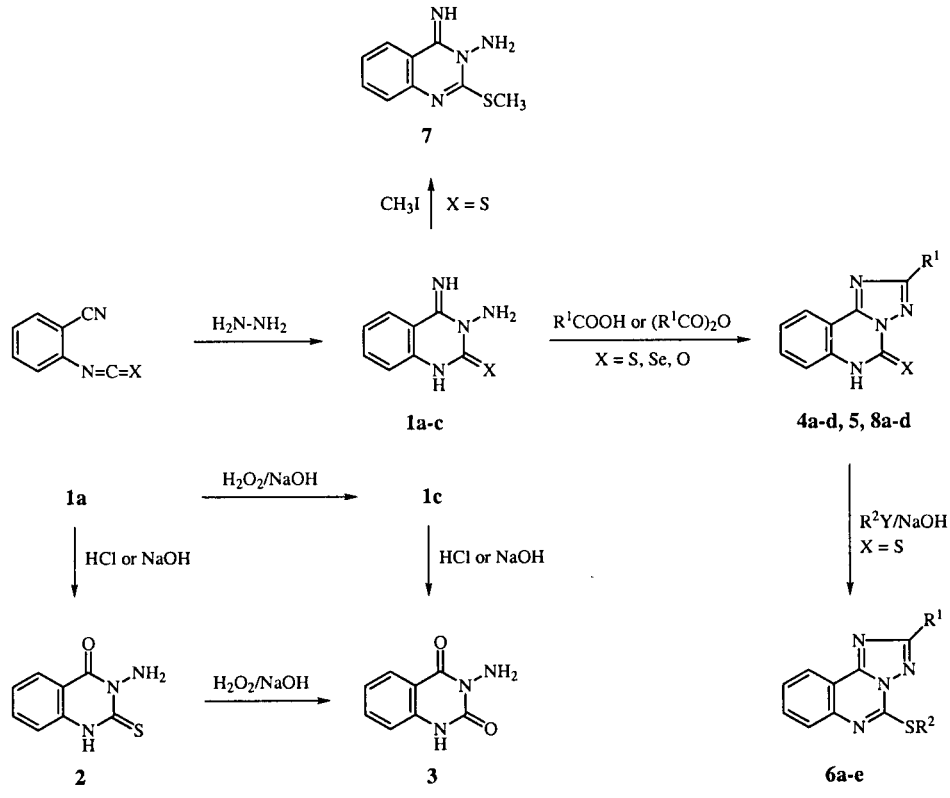
2-Isothiocyanato- [15], 2-isoselenocyanato- [16] and 2-isocyanatobenzonitrile [29], respectively, were available precursors for the syntheses of the quinazoline derivatives **1a, 1b** and **1c**. These starting materials reacted *in situ* with hydrazine hydrate to chalcogenocarbazides which cyclized to **1a-c** spontaneously. We prepared compound **1c** alternatively by oxidative desulfuration of **1a** using hydrogen peroxide. By increasing the reaction temperature, undesirable amounts of 3-amino-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**3**) were isolated. The identity of **3** was confirmed by an independent synthesis, *i.e.* by oxidative desulfuration of 3-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline (**2**) using hydrogen peroxide in basic medium. Quinazoline **2** was prepared from methyl 2-isothiocyanatobenzoate and hydrazine hydrate [17], or alternatively, by reaction of 2-amino-benzhydrazide with carbon disulfide in the presence of base [18]. Furthermore, **2** was prepared in very good yield by hydrolysis of 3-amino-4-imino-2-thioxo-1,2,3,4-tetrahydroquinazoline (**1a**) with concentrated hydrochloric acid and subsequent treatment with 10% sodium hydroxide solution. This method has not been reported.

The cyclocondensation of 3-amino-4-imino-2-thioxo-1,2,3,4-tetrahydroquinazoline (**1a**) and their 2-selenoxo **1b** as well as the 2-oxo analogue **1c**, respectively, with carboxylic acids, carboxylic anhydrides, triethyl orthoformate and orthoacetate proceeds by formation of 2-substituted 5-thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines **4a-d**, 2-methyl-5-selenoxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline **5**, and 2-substituted 5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines **8a-d**. These compounds were deprotonated by sodium hydroxide to form salts soluble in the reaction medium. The formation of 1,3,4-chalcogenodiazolo[2,3-*b*]quinazoline derivatives was not observed.

The proposed structures of the 1,2,4-triazolo[1,5-*c*]-quinazolines **4a-d, 5, 8a-d** were confirmed by ^{1}H- and ^{13}C-nmr spectroscopy (Tables 1, 2) and by their chemical properties (*cf.* Scheme 1 and 2). First, **4a, 4c** reacted with alkylating agents in the presence of sodium hydroxide to 5-alkylsulfanyl-1,2,4-triazolo[1,5-*c*]quinazolines **6a-e**. Analogously, starting compound **1a** was converted with methyl iodide to 3-amino-4-imino-2-methylsulfanyl-3,4-dihydroquinazoline (**7**).

Furthermore, 5-thioxo-5,6-dihydro-1,2,4-triazolo-[1,5-*c*]quinazolines **4a-d** were desulfurized with 30% hydrogen peroxide solution in basic medium at room temperature to form the oxo analogues, 5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines **8a-d**. Presumably, this

Scheme 1



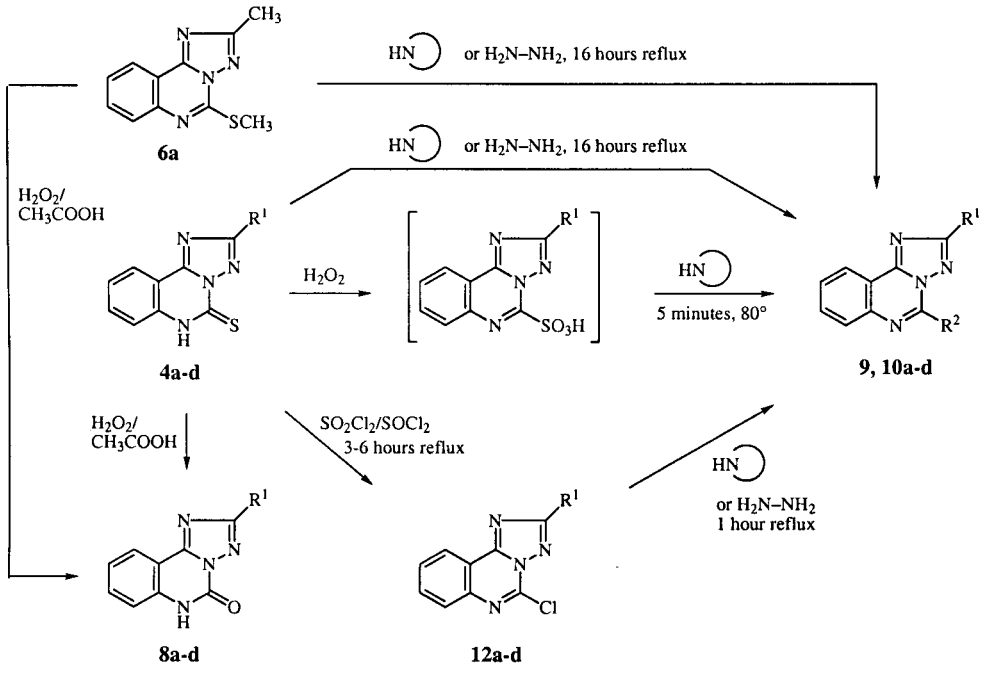
	R^1	R^2	X		R^1	R^2	X
1a	-	-	S	**6b**	H	CH_3	-
1b	-	-	Se	**6c**	CH_3	$CH_2C_6H_5$	-
1c	-	-	O	**6d**	CH_3	CH_2-COOH	-
4a	CH_3	-	S	**6e**	CH_3	CH_2-CH=CH_2	-
4b	C_2H_5	-	S	**8a**	CH_3	-	O
4c	H	-	S	**8b**	C_2H_5	-	O
4d	CF_3	-	S	**8c**	H	-	O
5	CH_3	-	Se	**8d**	CF_3	-	O
6a	CH_3	CH_3	-				

type of reaction proceeds *via* oxidation of the thioxo to a sulfonato group which hydrolyzes with hydroxide to the oxo group of **8a-d**. By an independent synthesis starting with 2-(5-trifluoromethyl-4*H*-1,2,4-triazol-3-yl)benzoic acid, ethyl chlorocarbonate and sodium azide *via* intermediate isocyanate, the structure **8d** was confirmed [19].

It was reported that 2-alkylsulfanyl-3-aryl-4-oxo-3,4-dihydroquinazolines were transformed by hydrogen peroxide in acetic acid solution to the corresponding 2-(alkylsulfonyl)-3-aryl-4-oxo-3,4-dihydroquinazolines [20]. In contrast to this, we found that 2-methyl-5-methylsulfanyl-1,2,4-triazolo[1,5-*c*]quinazoline (**6a**) reacted to form 2-methyl-5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**8a**) under the same reaction conditions. We explained this by an initial formation of the corresponding sulfone which hydrolyzed to the methanesulfonic acid and **8a**. We did not observe direct hydrolytic cleavage of methanthiole from **6a** and formation of **8a**.

The hydrazinolysis of thioxoquinazolines has already been reported [21-25]. The hydrazinolysis of 5-thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline **4a** to 5-hydrazino-2-methyl-1,2,4-triazolo[1,5-*c*]quinazoline **9** was accomplished in very good yield and high purity by treatment with a 40-fold excess of hydrazine hydrate in ethanol solution at reflux temperature over a period of 16 hours. Similarly, aminolyses of **4a** and **4b**, respectively, with secondary amines yielded 5-morpholino-, 5-piperidino-, 5-pyrrolidino-3-methyl-1,2,4-triazolo[1,5-*c*]quinazolines **10a-c**, and the 5-morpholino-3-ethyl-1,2,4-triazolo[1,5-*c*]-quinazoline (**10d**), respectively. Additionally 2-methyl-5-methylsulfanyl-1,2,4-triazolo[1,5-*c*]quinazoline (**6a**) and 5-chloro-1,2,4-triazolo[1,5-*c*]quinazolines **12a-c** were used

Scheme 2



	R^1	R^2
9	CH_3	-NH-NH_2
10a	CH_3	morpholino
10b	CH_3	piperidino
10c	CH_3	pyrrolidino
10d	C_2H_5	morpholino
12a	CH_3	
12b	C_2H_5	
12c	H	
12d	CF_3	

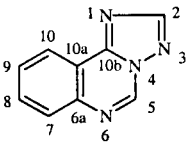
as starting material for the syntheses of **9** and **10a-c**. The latter mentioned starting material was prepared either from the 5-thioxo derivatives **4a-c** by reaction with sulfonyl chloride, or a sulfonyl chloride/thionyl chloride mixture, respectively. The syntheses of the pure 5-chloroquinazolines **12a-c** were not generally possible. During the work-up procedure, the hydrolysis to 5-oxo-5,6-dihydro-1,2,4-triazolo-[1,5-*c*]quinazolines has proceeded partially. Hydrazinolysis or aminolysis of **12a, 12b** with hydrazine hydrate and secondary amines, respectively, yielded compounds **9** and **10a-d** in good yields and without formation of any detectable by-products.

We also found a new excellent method for the preparation of the amino compounds **10a-d** from the thioxo derivatives **4a,b** by reaction with secondary amines in the presence of hydrogen peroxide. These reactions proceed probably *via* oxidation of the thioxo groups into intermediate sulfonato groups, followed by nucleophilic substitution of these good leaving groups by amines (Scheme 2). Analogous reactions of **4a** with primary amines did not yield the expected 5-alkyl(aryl)amino-2-methyl-1,2,4-triazolo[1,5-*c*]-quinazolines, but the 2-oxo derivative **8a** in all instances.

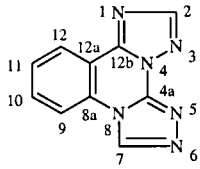
As already mentioned, compound **9** is a suitable precursor for syntheses of tetracyclic fused heterocycles. Thus, the heterocyclic amidrazone **9** was transformed by reaction with formic acid, acetic acid, acetic anhydride and propanoic anhydride, respectively, into the bis-1,2,4-triazolo[4,3-*a*:1,5-*c*]quinazolines **13a-c**. Compound **13a** was prepared also from 3-amino-2-hydrazino-4-imino-3,4-dihydroquinazoline (**11**) on heating in triethyl orthoacetate over a period of 2 hours. Hydrazinolysis of **1a** formed **11**. The bis-1,2,4-triazolo[4,3-a:1,5-*c*]quinazolines **13a-c** have not been described until now. We found that product **13a** is not identical with the isomeric 3,7-dimethylbistriazolo-[4,3-*a*:4,3-*c*]quinazoline described by Potts *et al.* [10]. Physical and spectroscopic data (^{1}H-nmr) of **13a** revealed that both compounds are differently anellated bistriazoloquinazoline systems.

Table I

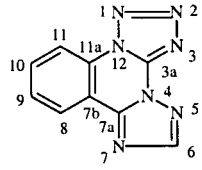
^{1}H-NMR Data [ppm] of **1a,b, 2,3,4a-d, 5, 6a-e, 7, 8a-d, 9, 10a-d, 11, 12a-d, 13a-c, 14**



4a-d, 5, 6a-e, 8a-d, 9, 10a-d, 12a-d



13a-c



14

Compounds

1a [a]	7.23-9.35 (m, 6H, ArH, 2NH), 6.54 (s, 2H, NH_2)
1b [a]	8.66 (s, 2H, 2NH), 7.21-8.20 (m, 4H, ArH), 6.53 (s, 2H, NH_2)
2 [a]	13.15 (s, 1H, 1NH), 7.34-8.01 (m, 4H, ArH), 6.38 (s, 2H, NH_2)
3 [a]	11.62 (s, 1H, 1NH), 7.83-9.19 (m, 4H, ArH), 5.50 (s, 2H, NH_2)
4a [a]	13.80 (s, 1H, 1NH), 8.22 (d, 1H, C_{10}-H, J = 8.1 Hz), 7.43-7.77 (m, 3H, Ar-H), 2.63 (s, 3H, CH_3)
4b [b]	11.40 (s, 1H, 1NH), 8.40 (d, 1H, C_{10}-H, J = 8.1 Hz), 7.45-7.74 (m, 3H, ArH), 3.03 (q, 2H, CH_2), 1.48 (t, 3H, CH_3)
4c [a]	14.03 (s, 1H, 1NH), 8.64 (s, 1H, C_2-H), 8.21 (d, 1H, C_{10}-H, J = 7.8 Hz), 7.5-7.81 (m, 3H, Ar-H)
4d [b]	11.30 (s, 1H, 1NH), 8.43 (d, 1H, C_{10}-H, J = 8 Hz), 7.46-7.78 (m, 3H, ArH)
5 [b]	11.10 (s, 1H, 1NH), 8.34 (d, 1H, C_{10}-H, J = 8.1 Hz), 7.27-7.70 (m, 3H, ArH), 2.70 (s, 3H, CH_3)
6a [b]	8.40 (d, 1H, C_{10}-H, J = 8 Hz), 7.26-7.94 (m, 3H, Ar-H), 2.81 (s, 3H, C_2-CH_3), 2.96 (s, 3H, S-CH_3)
6b [b]	8.45 (d, 1H, C_{10}-H, J = 8.3 Hz), 8.40 (s, 1H, C_2-H). 7.70-7.97 (m, 3H, Ar-H), 2.83 (s, 3H, S-CH_3)
6c [b]	8.41 (d, 1H, C_{10}-H, J = 8 Hz), 7.58-7.98 (m, 3H, Ar-H), 7.24-7.55 (m, 5H, ArH of Bn), 4.69 (s, 2H, CH_2 of Bn), 2.67 (s, 3H, C_2-CH_3)
6d [a]	13.02 (s, 1H, OH), 8.31 (d, 1H, C_{10}-H, J = 7.7 Hz), 7.66-7.89 (m, 3H, Ar-H), 4,26 (s, 2H, CH_2), 12.59 (s, 3H, C_2-CH_3)
6e [b]	8.42 (d, 1H, C_{10}-H, J = 8 Hz), 7.60-7.97 (m, 3H, Ar-H), 6.04-6.13 (m, 1H, =CH_2), 5.22-5.50 (m, 2H, =CH_2), 4.10-4.13 (d, 2H, S-CH_3), 2.70 (s, 3H, C_2-CH_3)
7 [a]	7.28-8.09 (m, 4H, Ar-H), 5.78 (s, 2H, NH_3), 2.38 (s, 3H, CH_3)
8a [a]	12.20 (s, 1H, 1NH), 8.08 (d, 1H, C_{10}-H, J = 8.5 Hz), 7.34-7.70 (m, 3H, Ar-H), 2.52 (s, 3H, CH_3)
8b [a]	12.20 (s, 1H, 1NH), 8.11 (d, 1H, C_{10}-H, J = 8.5 Hz), 7.34-7.70 (m, 3H, Ar-H), 2.86 (q, 2H, CH_3), 1.34 (t, 3H, CH_3)
8c [a]	12.34 (s, 1H, 1NH), 8.52 (s, 1H, C_2-H), 8.07 (d, 1H, C_{10}-H, J = 8.5 Hz), 7.37-7.91 (m 3H, Ar-H, 1CH)
8d [a]	12.40 (s, 1H, 1NH), 8.21 (d, 1H, C_{10}-H, J = 8.5 Hz), 7.32-7.81 (m 4H, Ar-H)
9 [a]	9.18 (s, 1H, 1NH), 8.16-8.19 (d, 1H, C_{10}-H), 7.70-7.73 (d, 1H, C_7-H), 7.64-7.68 (t, 1H, C_9-H), 7.37-7.41 (t, 1H, C_8-H), 4.64 (s, 2H, NH_2), 2.56 (s, 3H, CH_3)
10a [b]	7.39-8.33 (m, 4H, Ar-H), 4.02-4.05 (t, 4H, O-CH_2), 3.92-3.96 (t, 4H, N-CH_2), 2.64 (s, 3H, CH_3)
10b [b]	7.40-8.34 (m, 4H, ArH), 4.07-4.12 (t, 4H, N-CH_2); 2.65 (s, 3H, CH_2), 1.61-1.83 (m, 6H, CH_2)
10c [b]	7.58-8.26 (m, 4H, ArH), 4.07-4.12 (t, 4H, 2N-CH_2), 2.61 (s, 3H, CH_2), 2.00-2.05 (m, 4H, CH_2)
10d [b]	7.40-8.37 (m, 4H, ArH), 4.03-4.08 (t, 4H, O-CH_2), 3.93-3.96 (t, 4H, NCH_2), 2.96-3.03 (q, 2H, 2-CH_2), 1.42-1.48 (t, 3H, CH_2)
11 [a]	9.27 (s, 1H, N-H), 6.99-7.90 (m, 5H, 4Ar-H, NH), 4.22-4.63 (d, 4H, NH_2)
12a [a]	8.42 (d, 1H, C_{10}-H, J = 7.8 Hz), 7.25-7.81 (m, 3H, Ar-H), 2.75 (s, 3H, CH_3)
12b [a]	9.07 (d, 1H, C_{10}-H, J = 7.8 Hz). 7.86-8.22 (m, 3H, Ar-H), 3.28 (q, 2H, CH_2, J = 7.5 Hz), 1.59 (t, 3H, CH_2, J = 7.5 Hz)
12c [a]	9.02 (d, 1H, C_{10}-H, J = 8 Hz), 8.61 (s, C_2-H), 7.52-8.22 (m, 3H, Ar-H)
12d [a]	8.89 (d, 1H, C_{10}-H, J = 8.8 Hz), 7.50-8.02 (m, 3H, Ar)
13a [a]	8.30-8.41 (m, 2H, C_9-H, C_{12}-H), 7.90-7.94 (t, 1H, C_{10}-H), 7.70-7.75 (t, 1H, C_{11}-H), 3.01 (s, 3H, C_7-CH_3), 2.57 (s, 3H, C_2-CH_3)
13a [b]	8.15-8.59 (m, 2H, C_9-H, C_{12}-H), 7.82-7.88 (t, 1H, C_{10}-H), 7.68-7.73 (t, 1H, C_{11}-H), 3.12 (s, 3 H, C_7-CH_3), 2.70 (s, 3 H, C_2-CH_3)
13b [b]	8.10-8.56 (m, 2H, C_9-H, C_{12}-H), 7.81-7.87 (t, 1H, C_{10}-H), 7.65-7.70 (t, 1H, C_{11}-H), 3.46 -3.89 (q, 2H, CH_3) 2.69 (s, 3H, C_2-CH_3), 1.68-1.63 (t, 3H, CH_3)
13c [a]	9.89 (s, 1H, C_7-H), 8.35-8.43 (m, 2H, C_9-H, C_{12}-H), 7.90-7.92 (t, 1H, C_{10}-H), 7.70-7.75 (t, 1H, C_{11}-H), 2.58 (s, 3H, CH_3)
14 [a]	8.50-8.56 (m, 2H, C_8-H, C_{11}-H), 8.05-8.11 (t, 1H, C_9-H), 7.88-7.93 (t, 1H, C_{10}-H), 2.58 (s, 3H, CH_3)

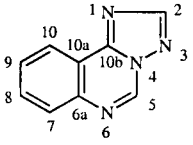
[a] In dimethyl-d_6 sulfoxide. [b] In deuteriochloroform.

Transformation of **9** with nitrous acid at -5 to 0° provided a new tetracyclic ring system, 6-methyltetrazolo[1,5-*a*][1,2,4]-triazolo[1,5-*c*]quinazoline (**14**) in almost quantitative yield. A study of azido-tetrazolo isomerization in substituted tetrazolo[1,5-*c*]quinazolines is reported in literature [26]. We were not able to find any vibration band of the azido groups of 5-azido-2-methyl-1,2,4-triazolo[1,5-*c*]quinazoline in the ir spectrum (FT) of **14** in chloroform. This observation showed that the anellated tetrazole ring in **14** is relatively stable.

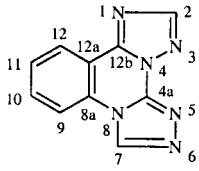
The ring closure of the hydrazine derivative **9** with C-1-synthons or nitrous acid causes considerable chemical shift changes of 9-H of **13** and 11-H of **14** (*cf.* Scheme 3). Thus, the signals of 9-H of **13c** and of 11-H of **14** were shifted 0.68 ppm and 0.82 ppm to lower field in comparison with 7-H of **9**. Therefore doublets of 9-H and 12-H of **13c** as well as of 8-H and 11-H of **14** are partially overlapped. By ^{1}H-nmr spectroscopy the alternative structure **A** (*cf.* Scheme 3) was excluded.

Table 2

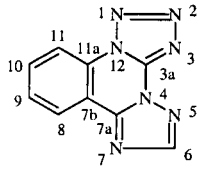
^{13}C-NMR Data [ppm] of **4a,c, 6a,c,d, 8a, 9, 10a, 12b-d, 13a-c, 14**



4a,c, 6a,c,d, 8a-d, 9, 10a, 12b-d



13a-c



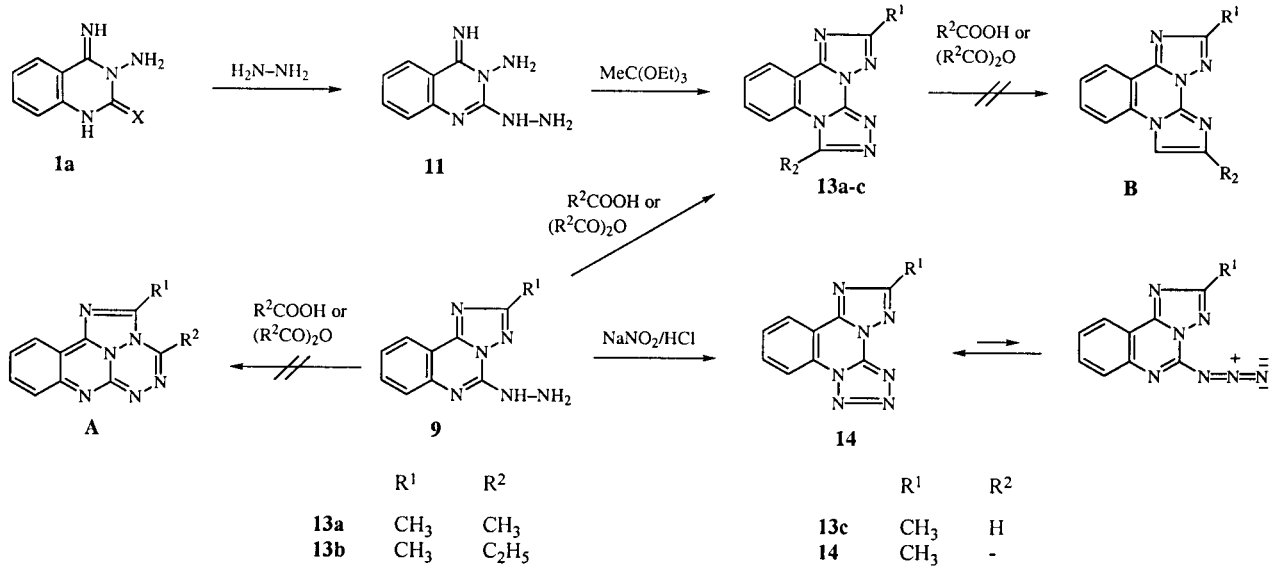
14

Compounds

4a [a]	171.0 (C_5), 169.5 (C_2), 153.7 (C_{10b}), 141.3 (C_{6a}), 137.6, 130.1, 128.9, 121.4 (C_7, C_8, C_9, C_{10}). 116.9 (C_{10a}), 19.3 (CH_3)
4c [a]	172.0 (C_5), 159.8 (C_2), 153.5 (C_{10b}), 141.3 (C_{6a}), 138.1, 130.6, 129.1, 121.4 (C_7, C_8, C_9, C_{10}), 117.5 (C_{10a})
6a [b]	164.0 (C_5), 150.7 (C_2), 149.2 (C_{10b}), 143.4 (C_{6a}), 131.9, 127.2, 127.0, 123.5 (C_7, C_8, C_9, C_{10}), 115.6 (C_{10a}), 14.6 (CH_3), 13.4 (SCH_3)
6c [b]	164.0 (C_5), 150.8 (C_2), 148.3 (C_{10b}), 143.4 (C_{6a}), 136.4 (C_1-Bn), 132.0, 129.4, 128.6, 127.7, 127.3, 127.1, 123.6 (C_7, C_8, C_9, C_{10}, C_2-Bn, C_3-Bn, C_4-Bn, C_5-Bn, C_6,-Bn), 34.8 (CH_2), 14.6 (CH_3)
6d [a]	169.6 (CO), 163.7 (C_5), 150.2 (C_2), 148.0 (C_{10b}), 142.7 (C_{6a}), 132.5, 127.7, 127.1, 123.5 (C_7, C_8,, C_9, C_{10}), 115.4 (C_{10a}), 33.0 (CH_2), 144 CH_3)
8a [a]	163.1 (C_5), 152.9 (C_2), 143.9 (C_{10b}), 137.1 (C_{6a}), 132.7, 124.1, 123.7, 123.7 (C_7, C_8, C_9, C_{10}), 110.3 (C_{10a}), 14.3 (CH_3)
9 [a]	162.9 (C_5), 151.4 (C_2), 145.2 (C_{10b}), 144.6 (C_{6a}), 132.2, 125.4, 123.4 (C_7, C_8, C_9, C_{10}). 113.3 (C_{10a}), 14.4 (CH_3)
10a [b]	162.6 (C_5), 153.8 (C_2), 144.7 (C_{10b}), 143.7 (C_{6a}), 132.0, 126.2, 125.0, 123.4 (C_7, C_8, C_9, C_{10}). 114.7 (C_{10a}), 66.6 (C_2-Morpholino, C_6-Morpholino), 48.2 (C_3-Morpholino, C_5-Morpholino). 14.55 (CH_3)
12b [b]	145.1, 145.0 (C_5, C_2), 136.1 (C_{10b}), 136.0 (C_{6a}), 130.4. 130.1, 128.3, 128.2 (C_7, C_8, C_9, C_{10}), 126.6 (C_{10a}), 20.8 (CH_2), 11.5 (CH_3)
12c [a]	148.7. 146.1 (C_5, C_2), 136.6 (C_{10b}), 133.3 (C_{6a}), 128.4, 125.8, 124.3, 123.4 (C_7, C_8, C_9, C_{10}), 120.6 (C_{10a})
12d [a]	158.8, 154.0 (C_5, C_2), 146.1 (C_{10b}), 145.3 (C_{6a}), 136.3, 129.1, 128.1, 126.7 (C_7, C_8, C_9, C_{10}), 122.3 (CF_3, $J_{C,F}$ = 281 Hz), 110.9 (C_{10a})
13a [a]	163.7 (C_{4a}), 149.1 (C_2), 147.3 (C_{12b}), 143.3 (C_{8a}), 113.0 (C_{12a}), 132.8, 131.7, 127.3, 125.6, 117.0 (C_7, C_9, C_{10}, C_{11}, C_{12}), 113.4 (C_{12a}), 15.3 (C_8-CH_3) 14.2 (C_2-CH_3)
13b [b]	165.1 (C_{4a}), 151.5 (C_2), 148.8 (C_{12b}), 143.4 (C_{8a}), 132.5, 131.5, 127.4, 126.6, 116.1 (C_7, C_9, C_{10}, C_{11}, C_{12}), 113.7 (C_{12a}), 23.0 (CH_2), 14.3 (CH_3) 11.0 (CH_3)
13c [a]	163.6 (C_{4a}), 149.4 (C_2), 147.4 (C_{12b}), 137.2 (C_{8a}), 132.9, 130.4, 127.7, 125.4, 116.9 (C_7, C_9, C_{10}, C_{11}, C_{12})
14 [a]	164.4 (C_{3a}), 150.7 (C_2), 145.1 (C_{7a}), 133.5, 129.9, 129.2, 125.2, 116.3 (C_8, C_9, C_{10}, C_{11}, C_{11a}), 112.9 (C_{7b}), 13.9 (C_2-CH_3)

[a] In dimethyl-d_6 sulfoxide. [b] In deuteriochloroform.

Scheme 3



The rearrangement of 1,2,4-triazolo[4,3-*a*]quinazolines into the corresponding 1,2,4-triazolo[1,5-*a*]quinazoline isomers has not been reported [22, 27, 28]. Our attempts to isomerize compounds **13a-c** into the bis-1,2,4-triazolo-[1,5-*a*:1,5-*c*]quinazolines **B** (*cf.* Scheme 3) by reaction with carboxylic acids and their anhydrides, respectively, failed.

Analogous to compound **14**, the larger magnetic anisotropy effect of the N-N bond of the [1,5-*a*]-anelleted 1,2,4-triazole ring of structure **B** should cause a larger downfield shift of the 9-H doublet which was not observed.

EXPERIMENTAL

Melting points are uncorrected, using a Boetius plate. The ^{1}H-nmr and ^{13}C-nmr, were obtained on a Bruker Model ARX 300-spectrometer and on a Bruker AVANCE DRX-500-spectrometer, respectively; in dimethyl-d_6 sulfoxide or deuteriochloroform with tetramethylsilane as internal standard. The following compounds were obtained by literature procedures; 3-amino-4-imino-2-thioxo-1,2,3,4-tetrahydroquinazoline (**1a**) from 1-cyano-2-isothiocyanatobenzene and hydrazine hydrate in dichloromethane [15], 3-amino-4-imino-2-selenoxo-1,2,3,4-tetrahydroquinazoline (**1b**) from 1-cyano-2-isoselenocyanatobenzene and hydrazine hydrate in dichloromethane [16], and 3-amino-4-imino-2-oxo-1,2,3,4-tetrahydroquinazoline (**1c**) from 1-cyano-2-isocyanatobenzene and hydrazine hydrate in tetrahydrofuran [29].

3-Amino-4-imino-2-oxo-1,2,3,4-tetrahydroquinazoline (**1c**).

Compound **1a** (1.92 g, 10 moles) was dissolved in 5% sodium hydroxide solution (50 ml). Hydrogen peroxide (30% 10 ml) was added dropwise into the solution at room temperature. The reaction mixture was then neutralized with acetic acid, the precipitate filtered and washed with water, yield 1.5 g (85%). Recrystallization from ethanol yielded **1c** as colorless needles, mp 260-262°, mp [29] 260-262°.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.61; H, 4,61; N, 31.85.

3-Amino-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline (**2**).

Method A.

Compound **1a** (1.92 g, 10 mmoles) was refluxed in concentrated hydrochloric acid (120 ml) for 7.5 hours. The mixture was first treated with sodium hydroxide solution until *p*H 8, and then with acetic acid to adjust to *p*H 7. The precipitate which formed was filtered and washed with water, yield 1.70 g (88%). Recrystallization from ethanol gave **2** as colorless needles, mp 199-200°, mp [17] 227°, mp [18] 188-190°.

Method B.

Compound **1a** (1.92 g, 10 mmoles) was dissolved in 10% sodium hydroxide solution (125 ml). The resulting mixture was then refluxed for 4.5 hours and neutralized with acetic acid. The precipitate was filtered and recrystallized from ethanol, yield 1.62 g (84%).

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.76. Found: C, 49.81; H, 3,71; N, 21.53.

3-Amino-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**3**).

Method A.

Quinazolinthione **2** (0.96 g, 5 mmoles) was dissolved in 5% sodium hydroxide solution (10 ml) at room temperature. Then 30% hydrogen peroxide (10 ml) was added dropwise and the mixture neutralized with acetic acid. Stirring was continued for 30 minutes. Precipitate **3** was isolated by suction filtration and washed with water, yield 0.82 g (93%). Recrystallization from ethanol yielded **3** as colorless needles, mp 291-292°, mp [29] 290-292°.

Method B.

Quinazolinthione **1c** (1.76 g, 10 mmoles) was refluxed in 10% sodium hydroxide solution (50 ml) for 1 hour. The mixture was neutralized with acetic acid, and the precipitated product was washed with water, yield 1.6 g (90%).

Method C.

Compound **1c** (1.76 g, 10 mmoles) was refluxed in concentrated hydrochloric acid (120 ml) for 6 hours. Further workup as described for compound **2**, method A, yielded 1.55 g (8.7%).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.48; H, 4.01; N, 23.97.

2-Substituted 5-Thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines **4a-d** and 2-Methyl-5-selenoxo-5,6-dihydro-1,2,4-triazolo-[1,5-*c*]quinazoline (**5**).

General Procedure (Method A).

Compounds **1a** (1.92 g, 10 mmoles) and **1b** (2.39 g, 10 mmoles), respectively, were refluxed in the requisite carboxylic anhydride (40 ml) for 2 hours. For the preparation of **4c, 1a** was boiled in anhydrous formic acid (15 ml) for 3 hours. Compound **1a** was refluxed in trifluoroacetic acid (50 ml) for 4 hours and yielded **4d**. The solution was filtered hot. The precipitated product that separated on cooling was filtered and washed with water.

Compounds **4a-d** and **5** were preparated following the general procedure (Method A). Alternatively, **4a** was formed by cyclocondensation with ethyl orthoacetate (Method B).

2-Methyl-5-thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**4a**).

Method A.

This compound was obtained from **1a** (1.92 g, 10 mmoles) and acetic anhydride (40 ml), yield 1.81 g (84%). Recrystallization from ethanol gave colorless needles, mp 284-285° dec.

Method B.

The compound **1a** (1.92 g, 10 mmoles) was refluxed in 2-propanol (200 ml) and ethyl orthoacetate (10 ml) for 10 hours. The resultant solution was concentrated *in vacuo* to 20 ml, yield 1.58 g (73%).

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91. Found: C, 55.49; H, 3,85; N, 25.86.

2-Ethyl-5-thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**4b**).

Method A.

This compound was obtained from **1a** (1.92 g, 10 mmoles) and propionic acid anhydride (40 ml), yield 1.75 g (76%). Recrystallization from ethanol gave colorless rods, mp 277-278° dec.

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.42; H, 4.52; N, 24.18.

5-Thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**4c**).

Method A.

This compound was obtained from **1a** (1.92 g, 10 mmoles) and anhydrous formic acid (15 ml), yield 1.74 g (86%). Recrystallization from methanol yielded colorless prisms, mp 325-328 dec.

Anal. Calcd. for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70. Found: C, 53.41; H, 3,11; N, 27.67.

2-Trifluoromethyl-5-thioxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]-quinazoline (**4d**).

Method A.

This compound was obtained from **1a** (1.92 g, 10 mmoles) and trifluoroacetic acid (50 ml), yield 1.92 g (71%). Recrystallization from ethanol gave colorless needles, mp 232-233° dec.

Anal. Calcd. for $C_{10}H_5F_3N_4S$: C, 44.45; H, 1.86; N, 20.73. Found: C, 44.41; H, 2.01; N, 20.85.

2-Methyl-5-selenoxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]-quinazoline (**5**).

Method A.

This compound was obtained from **1b** (10 mmoles) and acetic anhydride (40 ml), yield 2.05 g (78%). Recrystallization from ethanol gave colorless needles, mp 288-289° dec.

Anal. Calcd. for $C_{10}H_8N_4Se$: C, 45.64; H, 3.06; N, 21.29. Found: C, 45.71; H, 3.32; N, 21.37.

2-Methyl-5-methylsulfanyl-1,2,4-triazolo[1,5-*c*]quinazoline (**6a**).

Compound **4a** (1.08 g, 5 mmoles) was dissolved in 0.02 *M* sodium hydroxide solution (30 ml). Methyl iodide (1 g, 7 mmoles) was added dropwise and the mixture was heated to 60° over a period of 5 minutes. The colorless precipitate that separated on cooling was filtered and washed with water to give 1.05 g (91%), colorless needles (ethanol), mp 147-148°.

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.42; H, 4.51; N, 24.17.

5-Methylsulfanyl-1,2,4-triazolo[1,5-*c*]quinazoline (**6b**).

Compound **6b** was prepared from **4c** (1.01 g, 5 mmoles) as mentioned in **6a**, yield 0.88 g (90%). Recrystallization from ethanol gave colorless prisms, mp 131-133°.

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91. Found: C, 55.65; H, 3.85; N, 25.95.

5-Benzylsulfanyl-2-methyl-1,2,4-triazolo[1,5-*c*]quinazoline (**6c**).

Compound **4a** (2.16 g, 10 mmoles) was dissolved in a 0.015 *M* of methanolic potassium hydroxide solution (90 ml). Small amounts of insoluble residues were removed by filtration. Benzylchloride (1.5 g, 12 mmoles) was then added to the alkaline solution. The mixture was heated at reflux for 5 minutes, during which time potassium chloride separated. The product crystallized after cooling and addition of water, yield 2.98 g (97%). Recrystallization from ethanol in the presence of active carbon gave **6c** as colorless prisms, mp 154-155°.

Anal. Calcd. for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29. Found: C, 66.71; H, 4.80; N, 18.40.

5-Carboxymethylsulfanyl-2-methyl-1,2,4-triazolo[1,5-*c*]-quinazoline (**6d**).

Compound **4a** (2.16 g, 10 mmoles) was dissolved in a 0.02 *M* sodium hydroxide solution (100 ml). Chloroacetic acid (2.36 g, 25 mmoles), neutralized with saturated aqueous sodium carbonate solution (4 ml), was added to the alkaline solution of **4a**. The mixture was allowed to stand 48 hours at room temperature and was then acidified with acetic acid to *p*H 5-6. A colorless precipitate formed which was washed with water, yield 2.64 g (96%), colorless prisms (ethanol), mp 252-256°.

Anal. Calcd. for $C_{12}H_{10}NO_2S$: C, 52.55; H, 3.67; N, 20.43. Found: C, 52.51; H, 3.75; N, 20.46.

5-Allylthio-2-methyl-1,2,4-triazolo[1,5-*c*]quinazoline (**6e**).

Compound **4a** (3.24 g, 15 mmoles) was dissolved in 0.05 *M* sodium hydroxide solution. Allylbromide (2 g, 16.5 mmoles) was added dropwise and the solution was stirred for 45 minutes at room temperature. The colorless precipitate was filtered and washed thoroughly with water, yield 3.52 g (96%), colorless prisms (ethanol), mp 234°.

Anal. Calcd. for $C_{13}H_{14}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.72; H, 4.93; N, 22.03.

3-Amino-4-imino-2-methylsulfanyl-3,4-dihydroquinazoline (**7**).

This compound was prepared from **1a** (0.96 g, 5 mmoles) and methyliodide (1 g, 7 mmoles) as described for **6a**. A precipitate formed which was filtered and washed with water to give 0.82 g (89%), colorless needles (ethanol), mp 145-148°.

Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.84; N, 27.16. Found: C, 52.53; H, 4.91; N, 26.94.

General Procedure for the Preparation of 5-Oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazolines 8**a-d**.

Method A.

Compounds **4a-c** (10 mmoles) were dissolved in 5% sodium hydroxide solution (50 ml). With stirring, 30% hydrogen peroxide solution (50 ml) was added at room temperature. The mixture was then acidified with acetic acid. The resultant precipitate was washed with water and recrystallized from ethanol.

Method B.

Compound **1c** (1.76 g, 10 mmoles) was refluxed in acetic anhydride, propionic acid anhydride, formic acid or trifluoroacetic anhydride, respectively, for 2-7.5 hours. The solvents were destilled *in vacuo* to a volume of *ca* 10 ml. The requisite precipitate that separated on cooling was removed by filtration.

Compounds **8a-c** were prepared by the general procedure (Method A), **8a-d** were prepared by the general procedure (Method B). Alternatively **8a** was obtained by reaction with 30% hydrogen peroxide solution (Method C).

2-Methyl-5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**8a**).

Method A.

This compound was obtained from **4a** (2.16 g, 10 mmoles) and 30% hydrogen peroxide solution, yield 1.64 g (82%). Recrystallization from 2-propanol yielded **8a** as colorless rods, mp 324-325°.

Method B.

Compound **1c** (1.76 g, 10 mmoles) and acetic anhydride (20 ml) was refluxed for 2 hours, yield 1.44 g (72%).

Method C.

Compound **6a** (1.15 g, 5 mmoles) was dissolved in acetic acid (10 ml), heated to boiling and treated dropwise with 30% hydrogen peroxide solution (10 ml). Then, hot water was added to the mixture. After cooling to room temperature, the colorless product was filtered and washed with water, yield 1.92 g (96%).

Anal. Calcd. for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 59.98; H, 4.12; N, 28.08.

2-Ethyl-5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**8b**).

Method A.

This compound was obtained from **4b** (2.3 g, 10 mmoles) and 30% hydrogen peroxide solution, yield 1.82 g (85%). Recrystallization from ethanol gave **8b** as colorless needles (ethanol), mp 273-275°.

Method B.

Compound **1c** (1.76 g, 10 mmoles) in propionic acid anhydride (20 ml) was refluxed 3 hours, yield 1.6 g (75%).

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.85; H, 4.91; N, 26.43.

5-Oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**8c**).

Method A.

This compound was obtained from **4c** (2.02 g, 10 mmoles) and 30% hydrogen peroxide solution, yield 1.51 g (81%), colorless needles (ethanol), mp 309-311° dec.

Method B.

Compound **1c** (10 mmoles) in formic acid (80 ml) was refluxed for 4.5 hours, yield 1.45 g (78%).

Anal. Calcd. for $C_9H_9N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 58.26; H, 3.31; N, 30.24.

3-Trifluoromethyl-5-oxo-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**8d**).

Method A.

This compound was obtained from **4d** (2-7 g, 10 mmoles) and 30% hydrogen peroxide solution, yield 1.9 g (75%). Recrystallization from ethanol gave **8d** as pale yellow prisms, mp 295-296° dec, mp [19] 295-297°.

Method B.

A solution of **1c** (1.76 g, 10 mmoles) in trifluoroacetic anhydride (130 ml) was refluxed for 7.5 hours, yield 1.78 g (70%).

Anal. Calcd. for $C_{10}H_{5F3}N_4O$: C, 47.26; H, 1.98; N, 22.04. Found: C, 47.31; H, 2.12; N, 22.04.

5-Hydrazino-2-methyl-1,2,4-triazolo[1,5-*c*]quinazoline (**9**).

Method A.

Compound **4a** (1.08 g, 5 mmoles) was dissolved in a mixture of 100% hydrazine hydrate (10 ml) and ethanol (40 ml) and refluxed for 16 hours. The color of the mixture turned to yellow-green upon heating while hydrogen sulfide was generated. After cooling, a precipitate formed which was separated by filtration and washed with water, yield 0.9 g (84%). Recrystallization from ethanol yielded **9** as colorless prisms which formed needles at 175°, mp 225-227°.

Method B.

Compound **6a** (1.15 g, 5 mmoles) was dissolved in 100% hydrazine hydrate (25 ml) and ethanol (25 ml). Further preparation as described under A, yielded 1.03 g (96%).

Method C.

Compound **12a** (2.18 g, 10 mmoles) was heated at reflux in 100% hydrazine hydrate (25 ml) and ethanol (25 ml) for 3 hours. After cooling, a precipitate formed which was filtered and washed with water, yield 2 g (93%).

Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.07; H, 4.70; N, 39.23. Found: C, 56.14; H, 4.92; N, 38.94.

General Procedure for the Preparation of the 5-Substituted 1,2,4-Triazolo[1,5-*c*]quinazolines **10a-d**. Methods A, B.

Method A.

Compounds **4a** (2.16 g, 10 mmoles) **4b** (2.3 g, 10 mmoles) or **6a** (2.3 g, 10 mmoles), respectively, were dissolved at 70° in the secondary amine (12-14 ml) and ethanol (2 ml) and refluxed for 16 hours. 5-Chloroquinazolines **12a** (2.18 g, 10 mmoles) or **12b** (2.32 g, 10 mmoles), respectively, were refluxed with the secondary amine (12-14 ml) for 1 hour. After cooling to room temperature, the resultant product was filtered and washed with methanol.

Method B.

Compounds **4a** (1.08 g, 5 mmoles) and **4b** (1.15g, 5 mmoles), respectively were dissolved in the secondary amine (8 ml) at 80°. 30% hydrogen peroxide (5 ml) was added dropwise to the mixture. After cooling, the precipitate was filtered, washed with water, and recrystallized from methanol.

Compounds **10a-d** were prepared following the general procedures (Methods A, B).

2-Methyl-5-morpholino-1,2,4-triazolo[1,5-*c*]quinazoline (**10a**).

Method A.

This compound was obtained from **4a** (2.16 g, 10 mmoles) and morpholine (12 ml), yield 2.2 g (82%). Recrystallization from methanol yielded **10a** as colorless prisms, mp 126-127°. Analogously, **10a** was obtained from **6a** (2,3 g, 10 mmoles) and morpholine (12 ml), yield 2.13 g (79%). The reaction of **12a** (2.18 g, 10 mmoles) and morpholine (12 ml) affords **10a**, yield 2.2 g (82%)

Method B.

Compound **10a** was prepared from **4a** (2.16 g, 10 mmoles), morpholine (8 ml) and 30% hydrogen peroxide (5 ml), yield, 2.29 g (85%).

Anal. Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.51; H, 5.65; N, 26.28.

2-Methyl-5-piperidino-1,2,4-triazolo[1,5-*c*]quinazoline (**10b**).

Method A.

This compound was obtained from **4a** (2.16 g, 10 mmoles) and piperidine (14 ml), yield 2.27 g (85%). Recrystallization from methanol yielded **10b** as colorless rods, mp 129-130°. Analogously, **10b** was obtained from **6a** (2.3 g, 10 mmoles) and piperidine (14 ml), yield 2 g (75%). Compound **10b** was also obtained from **12a** (2.18 g, 10 mmoles) and piperidine (14 ml), yield 2.03 g (76%).

Method B.

Compound **4a** (2.16 g, 10 mmoles) reacted with piperidine (14 ml) and 30% hydrogen peroxide (5 ml) to give **10b**, yield 2.35 g (88%).

Anal. Calcd. for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.45; H, 6.52; N, 26.31.

2-Methyl-5-pyrrolidino-1,2,4-triazolo[1,5-*c*]quinazoline (**10c**).

Method A.

This compound was obtained from **4a** (2.16 g, 10 mmoles) and pyrrolidine (12 ml), yield 2.1 g (83%). Recrystallization from methanol gave **10c**, mp 166-167°. Analogously, **10c** was prepared from **6a** (2.3 g, 10 mmoles) and pyrrolidine (12 ml), yield 1.87 g (74%). Compound **10c** was also obtained from **12a** (2.18 g, 10 mmoles) and pyrrolidine (12 ml), yield 1.9 g (75%).

Method B.

Compound **10c** was formed from **4a** (2.16 g, 10 mmoles), pyrrolidine (12 ml) and 30% hydrogen peroxide (5 ml), yield 2.18 g (86%).

Anal. Calcd. for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.51; H, 6.01; N, 27.53.

2-Ethyl-5-morpholino-1,2,4-triazolo[1,5-*c*]quinazoline (**10d**).

Method A.

This compound was obtained from **4b** (2.3 g, 10 mmoles) and morpholine (14 ml), yield 2.23 g (79%). Recrystallization from methanol gave **10d**, mp 108-110°. Analogously, **10d** was obtained from **6b** (2.3 g, 10 mmoles) and morpholine (14 ml), yield 2.26 g (80%). The reaction of **12b** (2.32 g, 10 mmoles) and morpholine (14 ml) yielded 2.04 g (72%) of **10d**.

Method B.

This compounds was obtained from **4b** (2.3 g, 10 mmoles), morpholine (14 ml) and 30% hydrogen peroxide (5 ml), yield 2.4 g (85%).

Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.64; H, 24.93; N, 24.81.

3-Amino-2-hydrazino-4-imino-3,4-dihydroquinazoline (**11**).

Compound **1a** (3.84 g, 20 mmoles) was refluxed in a solution of 100% hydrazine hydrate (120 ml) and 2-propanol (5 ml) for 16 hours. Further work up as described for **9** gave **11**, yield 3.53 g (93%), colorless needles (methanol), mp 209-212° dec.

Anal. Calcd. for $C_8H_{10}N_6$: C, 50.52; H, 5.30; N, 44.18. Found: C, 50.52; H, 5.43; N, 43.98.

2-Methyl-5-chloro-1,2,4-triazolo[1,5-*c*]quinazoline (**12a**).

A stirred solution of **4a** in chloroform (70 ml) was treated with thionyl chloride (0,5 ml). Then sulfonylchloride (3.4 g, 25 mmoles) was added dropwise within of 5 minutes. Sulfur dioxide and hydrogen chloride were evolved. After heating at reflux for 6 hours, silica gel was added to the solution, which was filtered after 1 hour. Then the solution was reduced by distillation *in vacuo* to 10 ml. The resultant product was filtered and washed subsequently with dichloromethane then and petroleum ether, yield 3.6 g (83%). Recrystallization from xylene gave **12a** as colorless prisms, mp 250-252°.

Anal. Calcd. for $C_{10}H_7ClN_4$: C, 54.93; H, 3.23; N, 25.62. Found: C, 54.85; H, 3.51; N, 25.71.

2-Ethyl-5-chloro-1,2,4-triazolo[1,5-*c*]quinazoline (**12b**).

This compound was obtained from **4b** (4.60 g, 20 mmoles) in chloroforme (70 ml), sufonyl chloride (3.4 g, 25 mmoles) and thionylchloride (0.5 ml) as described for **12a**, yield 3.8 g (82%). Recrystallization from toluene gave **12b** as colorless prisms, mp 187-189°.

Anal. Calcd. for $C_{11}H_9ClN_4$: C, 56.78; H, 3.90; N, 24.08. Found: C, 56.68; H, 4.12; N, 24.14.

5-Chloro-5,6-dihydro-1,2,4-triazolo[1,5-*c*]quinazoline (**12c**).

This compound was obtained from **4c** (3.84 g, 20 mmoles) as described for **12a**, yield 3.6 g (89%). Recrystallization from thionyl chloride gave **12c** as colorless prisms, mp 277°.

Anal. Calcd. for $C_9H_5ClN_4$: C, 52.83; H, 2.46; N, 27.38. Found: C, 52.75; H, 2.51; N, 27.42.

2-Trifluoromethyl-5-chloro-1,2,4-triazolo[1,5-*c*jquinazoline (**12d**).

Compound **12d** was prepared from **4d** (5,4 g, 20 mmoles) as described for **12a**, yield 4.5 g (83%). Recrystallization from toluene/cyclohexane gave colorless prisms, mp 208-210°.

Preparation of the 7-Substituted 2-Methylbis-1,2,4-triazolo-[4,3-*a*:1,5-*c*]quinazolines **13a-c**.

General Procedure. Method A.

Compound **9** (1.07 g, 5 mmoles) and the carboxylic anhydride (5-10 ml) were heated in a water bath at 80° for 4 hours. The reaction of **9** with anhydrous formic acid (30 ml) or acetic acid (15 ml) was refluxed for 4 hours. Ice water was added after cooling of the mixture. The colorless precipitate formed was washed with water and recrystallized from the requisite solvent.

The following compounds were prepared by the general procedure which includes both Method A and Method B.

2,7-Dimethylbistriazolo[4,3-*a*:1,5-*c*]quinazoline (**13a**).

Method A.

This compound was obtained from **9** (1.07 g, 5 mmoles) and acetic acid (15 ml) or acetic anhydride (10 ml), yield 2.09 g (88%) and 2.02 g (85%), respectively. Recrystallization from ethanol gave **13a** as colorless needles, mp 325-326°.

Method B.

Compound **11** (1.90 g, 10 mmoles) was refluxed in ethyl orthoacetate (50 ml) for 2 hours. On cooling a precipitate of **13a** formed which was washed with water, yield 2.1 g (88%).

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.5; H, 4.23; N, 35.27. Found: C, 60.45; H, 4.45; N, 35.21.

2-Methyl-7-ethyl-bistriazolo[4,3-*a*:1,5-*c*]quinazoline (**13b**).

Method A.

This compound was prepared from **9** (1.07 g, 5 mmoles) and propionic acid anhydride (5 ml), yield 2.06 g (82%). Recrystallization from methanol gave **13b** as colorless needles, mp 311-312°.

Anal. Calcd. for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.31. Found: C, 61.80; H, 4.89; N, 31.13.

2-Methylbistriazolo[4,3-*a*:1,5-*c*]quinazoline (**13c**).

Method A.

Compound **9** (1.07 g, 5 mmoles) was refluxed in anhydrous formic acid (30 ml) for 4 hours, yield 1.84 g (82%). Recrystallization from methanol gave **13c** as colorless prisms, mp 332-335°.

Anal. Calcd. for $C_{11}H_8N_6$: C, 58.92; H, 3.60; N, 37.48. Found: C, 58.72; H, 3.71; N, 37.45.

6-Methyltetrazolo[1,5-*a*][1,2,4]triazolo[1,5-*c*]quinazoline (**14**).

With stirring a solution of sodium nitrite (0.5 g, 7.2 mmoles) in water (30 ml) was added dropwise at 0° to -5° into a mixture of **9** (1.07 g, 5 mmoles) in 10% hydrochloric acid (10 ml). A colorless precipitate formed which was washed with water, yield 0.9 g (80%). Recrystallization from ethanol gave **14** as colorless prisms, mp 212°.

Anal. Calcd. for $C_{10}H_7N_7$: C, 53.33; H, 3.13; N, 43.54. Found: C, 53.42; H, 3.19; N, 43.85.

REFERENCES AND NOTES

[1] S. Johne, *Pharmazie*, **36**, 583 (1981).

[2] P. C. Tang and G. Mcmahon, WO 9,640,648; *Chem. Abstr.*, **126**, 139911m (1997).

[3] G. S. Cockerill, M.C. Carter, S. K. Mckeown, S. Vile, M. J. Page, A. T. Hudson, P. Barraclough and K. W. Franzmann, WO 9,703,069 (1997); *Chem. Abstr.*, **126**, 199580n (1997).

[4] M. H. Yen, J. R. Sheu, I. H. Peng, Y. M. Lee and J. W. Chern, *J. Pharm. Pharmacol.*, **48**, 90 (1996).

[5] K. C. Liu and M. K. Hu, *Arch. Pharm. (Weinheim)*, **319**, 188 (1986).

[6] C. Cianci, T. D. Y. Chung, N. Menwell, H. Putz, M. Hagen, R. J. Colonno, and M. Krystal, *Antiviral Chem. Chemother.*, **7** (1996) 353.

[7] F. G. Kathawala, US Patent 3,847,918 (1974); *Chem. Abstr.*, **82**, 57724m (1975).

[8] F. G. Kathawala, US Patent 3,850,932 (1974); *Chem. Abstr.*, **82**, 140175d (1975).

[9] G. E. Hardtmann and F. G. Kathawala, US Patent 4,053,600 (1977); *Chem. Abstr.*, **88**, 22970k (1978).

[10] K. T. Potts and E. G. Brugel, *J. Org. Chem.* **95**, 3448 (1970); *Chem. Commun.*, **59**, 222 (1994).

[11] J. E. Francis, W. D. Cash, B. S. Barbaz, P. S. Bernard, R. A. Lovell, G. C. Mazzenga, R. C. Friedmann, J. L. Hyun, A. F. Braunwalder, P. S. Loo and D. A. Bennett, *J. Med. Chem.*, **34**, 281 (1991).

[12] K. Spirkova, J. Hornacek and S. Stankovsky, *Chem. Papers*, **47**, 382 (1993).

[13] W. Ried, and J. Valentin, *Chem. Ber.*, **101**, 2106 (1968).

[14] Y. A. Ammar, *Orient J. Chem.*, **6**, 165 (1990); *Chem. Abstr.*, **114**, 122249f (1991).

[15] P. Pazdera, E. Novacek and D. Ondracek, *Chem. Papers*, **43**, 465 (1989).

[16] W.-D. Pfeiffer, P. Pazdera, A. Hetzheim and J. Mücke, *Pharmazie*, **50**, 21 (1995).

[17] E. Cherbuliez, B. Willhalm, O. Espejo, S. Jaccard, and J. Rabinowitz, *Helv. Chim. Acta*, **50**, 2563 (1967).

[18] K.- C. Liu, M. K. Hu and Y. O. Lin, *Chung-hua Yao Hsueh Tsa Chih*, **42**, 83 (1990); *Chem. Abstr.* **114**, 23910h (1991).

[19] H. Reimlinger, F. Billiau, W. R. F. Lingier and M. A. Peiren, *Chem. Ber.*, **108**, 3799 (1975).

[20] R. P. Rao, B. Sharma and N. Zaidi, *Acta Cienc. Indica*, **4**, 254 (1978); *Chem. Abstr.*, **91**, 39422 (1979).

[21] K. Kottke and H. Kühmstedt, *Pharmazie* **37**, 635 (1982).

[22] K. Kottke, H. Kühmstedt and G. Grieser, *Pharmazie*, **38**, 367 (1983).

[23] S. Stanovsky and K. Spirkova, *Collect. Czech. Chem. Commun.* **49**, 1795 (1984)

[24] K. Kottke, H. Kühmstedt, I. Gräfe, P. Knoke, M. Schleuder, *Pharmazie*, **45**, 30 (1990).

[25] P. Richter and F. Oertel, *Pharmazie*, **45**, 721 (1990).

[26] S. Stanovsky and K. Spirkova, *Monatsh. Chem.*, **122**, 849 (1991).

[27] K. Kottke, H. Kühmstedt and D. Knoke, *Pharmazie*, **38**, 25 (1983).

[28] K. Kottke, Dissertation B, Universität Greifswald, 1985.

[29] G. Zinner, H. Klein, and H. Kahnert, *Chem.-Ztg.*, **111**, 341 (1987).