On Triazoles XLIX[1]. Synthesis of 5,6-Dihydrothiazolo[3,2-*b*]-[1,2,4]triazol-2-yl-, 6,7-Dihydro-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2-yl-, and 5,6,7,8-Tetrahydro[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2-yl-Isoquinolinium Salts

Ibolya Prauda and József Reiter

Egis Pharmaceuticals Ltd., P. O. Box 100, H-1475 Budapest, Hungary

Received July 24, 2003

5'-Mercapto-1'*H*-1,2,4-triazol-3'-yl-isoquinolinium salts (**6**) were synthesised by the reaction of *ortho*-acyl phenylacetones (**2**) or the corresponding pyrylium salts (**3**) and 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**5**). Treatment of thioles **6** with α,ω-dibromoalkanes led to type **15**, **16** and **17** isoquinolinium salts condensed with thiazole, thiazine and thiazepine rings. When **6** are reacted with dibromomethane (**10**) **11** type dimeric structures are obtained.

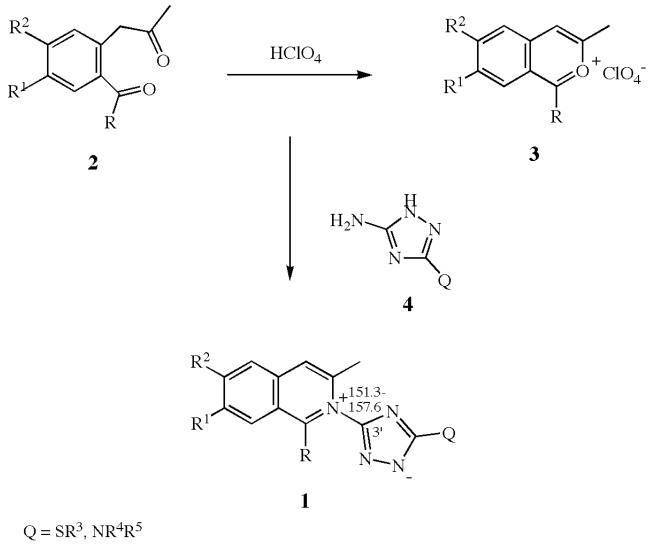
J. Heterocyclic Chem., **40**, 1041 (2003).

In a previous paper of this series [2] we have reported on the synthesis of **1** type 1,2,4-triazolyl isoquinolinium zwitter ions prepared from *ortho*-acyl phenylacetones (**2**) or the pyrylium salts (**3**) formed by reaction of compounds **2** with perchloric acid, followed by the corresponding 5-amino-3-Q-1*H*-1,2,4-triazoles (**4**) (Scheme 1).

As a continuation of the above studies the reactions of the *ortho*-acyl phenylacetones (**2**) and the corresponding pyrylium salts (**3**) with 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**5**) [3] were attempted to yield again a single product would have either the isoquinolinium structure (**6**) or the *S*-alkylated structure (**7**) depending on the reactivities of the amino and thione groups (Scheme 2).

The molecular weights of the isoquinolinium salts **6** and the *S*-alkylated derivatives **7** are different thus the structure **7** could be simply excluded on the basis of the mass spectra of the products obtained (Table I) pointing out to the presence of derivatives **6**. However, many attempts to purify the isoquinolinium salts **6** failed owing to their very low solubility and instability in solutions, and the fact that they appeared as not stoichiometric salts. This is the reason that in Table I besides the ms data no further analytical data are given. Structure **6** is also in agreement with the chemical shifts of the triazole carbon atoms 3' and 5' appearing as expected [2] between 153.8-156.9 ppm and 159.3-162.9 ppm, respectively (Scheme 2, Table Ia).

Scheme 1



Scheme 2

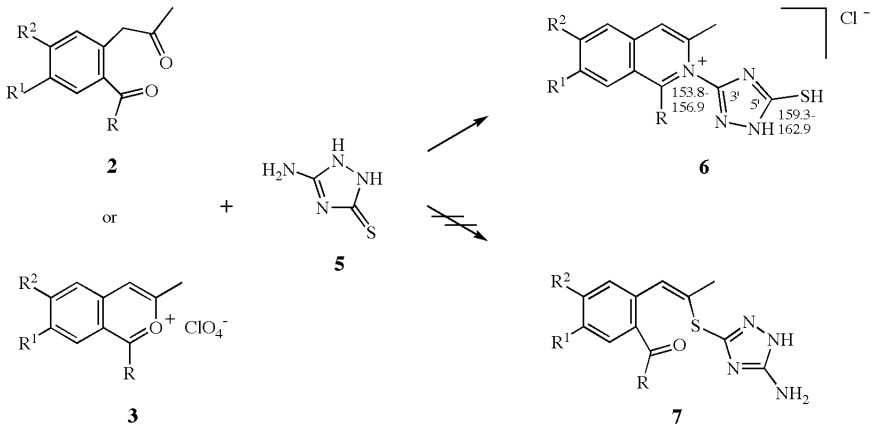


Table I

Synthetical Data of *N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium Chlorides (**6**)

Compound	R	R^1	R^2	Method Yield %	Mp (°C)	Ms (ES) M^+	Molecular formula (MW)	Molecular weight of the Isoquinolinium cation (M^+)
6/1	Propyl	Methylenedioxy		B 64	> 300	329	$C_{16}H_{17}ClN_4O_2S$ 364.86	329.41
6/2	4-(2-Propyl)-phenyl	Methoxy	Methoxy	A 99	213-216	421	$C_{23}H_{25}ClN_4O_2S$ 457.00	421.55
6/3	4-Fluoro-phenyl	Methoxy	Methoxy	A 95	185-190	397	$C_{20}H_{18}ClFN_4O_2S$ 432.91	397.46
6/4	4-Chloro-phenyl	Methoxy	Methoxy	A 82	188-193	413	$C_{20}H_{18}Cl_2N_4O_2S$ 449.36	413.91
6/5	4-Methoxy-phenyl	Methoxy	Methoxy	A 68	215-219	409	$C_{21}H_{21}ClN_4O_3S$ 444.94	409.49
6/6	3,4-Dimeth-oxy-phenyl	Methoxy	Methoxy	A 66	186-192	439	$C_{22}H_{23}ClN_4O_4S$ 474.97	439.52
6/7	4-Nitro-phenyl	Methoxy	Methoxy	A 68	212-215	424	$C_{20}H_{18}ClN_5O_4S$ 459.91	424.46

A preparative proof for structure **6** of the products obtained showed that *S*-alkylation reactions of **6** give products of type **1** identical with those obtained previously [2] by the ring closure of the *S*-alkyl triazoles (**4**) with the corresponding *ortho*-acyl phenylacetones (**2**) (Scheme 3, Tables II and IIa).

Derivatives **6** may exist in different tautomeric forms represented by structures **6a**-**6e** (Scheme 4). To answer the question of tautomerism their UV spectra were recorded in ethanolic, acidic and alkaline solution. The shape of the UV spectra do not change either in acidic or in alkaline solution, which is analogous with that observed for the *S*-alkylated derivatives **1** [2], thus excluding thiones **6a** and **6b**. Moreover from the above data, the presence of structures **6d** is deduced because the UV spectra of tautomers **6c** and **6e** would show a dramatic change in alkaline conditions [2].

To corroborate the above idea a **6b** type *N*-benzyl derivative **9** was synthesised as a model compound by structure proving synthesis starting from the corresponding **2** (R = 4-chlorophenyl, R^1, R^2 = methoxy) and 3-amino-4-benzyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**8**) [4] (Scheme 5). The carbon atom 5' of derivative **9** was shifted downfield to 169.1 ppm as compared with those of derivatives **6** appearing at 159.3-162.9 ppm pointing out its 5'-thione structure. As expected its UV spectrum, taken in alkaline solution, suffered a dramatic change as compared with those taken in ethanol and acidic media again in agreement with 5'-thione structure (See Experimental).

Having thioles **6** in hand their alkylation with dihaloalkanes was also attempted. The reaction of compounds **6** with dibromomethane (**10**) led to dimeric derivatives (**11**) (Scheme 6) as proved by their mass spectra and

Scheme 3

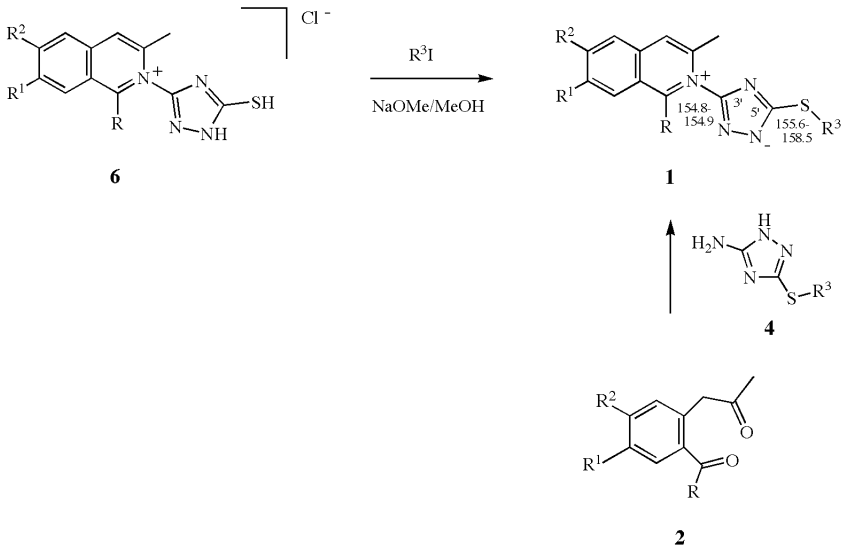


Table Ia

Pmr, Cmr (in δ ppm) and Uv spectral Data of Derivatives **6**

Compound	H-4	H-5 H-8	R	other	C-1	C-3 C-4	C-5 C-6	C-7 C-8	C-3' C-5'	R	other ArC	Ethanol λ_{max} ($\varepsilon.10^{-3}$)	10 % Ethanol + 90 % 0.1 *M* NaOH λ_{max} ($\varepsilon.10^{-3}$)	10 % Ethanol + 90 % 0.1 *M* HCl λ_{max} ($\varepsilon.10^{-3}$)
6/1	8.13 s	8.02 s	0.91 (t, 3H, J = 7.3 Hz)	2.41 (s, 3H)	160.0	143.7	103.5	151.5	172.3	14.0	19.5, 104.3	359sh (6.8)	355sh (6.9)	358sh (6.5)
		7.62 s	1.71 (m, 2H, J = 7.3 Hz)	6.46 (s, 2H)	[b,c]	122.7	156.7	103.0	153.8	23.8	122.3, 139.4	320 (15.7)	317 (13.9)	325 (15.5)
	[c]		2.89 (bs, 2H)							32.5		258 (64.5)	254 (64.3)	258 (67.4)
6/2	8.41 s	7.83 s	1.19 (s, 3H)	2.55 (s, 3H)	153.8	143.7	106.3	151.9	160.7	23.8, 33.7	20.1, 56.4	363 (6.4)	361 (6.6)	359sh (6.5)
		6.86 s	1.21 (s, 3H)	3.73 (s, 3H)		123.2	157.9	107.3	156.9	126.8, 127.0	57.8	327 (12.8)	321 (13.2)	334 (14.2)
	[c]		2.97 (qi, 1H)	4.15 (s, 3H)	[c]					130.6, 139.2	122.6	261 (51.2)	258 (53.2)	263 (48.1)
			7.40 (d, 2H, J = 8.6 Hz)								139.2			
			7.44 (d, 2H, J = 8.6 Hz)											
6/3	7.99 s	7.36 s	7.24 (dd, 2H, J = 8.4,	2.60 (s, 3H)	153.6	144.1	105.0	151.3	160.8	116.7 (d, 22.5 Hz)	19.9, 56.4	361sh (7.4)	355.5 (7.1)	358sh (9.2)
		6.81 s	8.6 Hz)	3.83 (s, 3H)		123.1	156.2	106.8	156.1	124.3 (d, 3.6 Hz)	57.4	326 (16.1)	322 (14.8)	331 (17.7)
	[a]		7.41 (dd, 2H, J = 5.1,	4.22 (s, 3H)	[a]					132.3 (d, 8.6 Hz)	122.9	262 (52.8)	259 (55.1)	262 (54.2)
			8.6 Hz)							164.0 (d, 251.0 Hz)	139.7			
6/4	8.04 s	7.43 s	7.35 (d, 2H, J = 8.6 Hz)	2.61 (s, 3H)	153.8	144.4	105.4	152.7	161.0	126.7, 127.0	19.8, 56.6	356sh (10.0)	362 (13.0)	358sh (9.6)
		6.90 s	7.56 (d, 2H, J = 8.6 Hz)	3.88 (s, 3H)		123.4	156.5	107.9	155.0	139.6, 140.3	57.5	333 (16.9)	327 (10.5)	332 (17.9)
	[d]			4.25 (s, 3H)	[d]						123.3, 139.6	262 (50.5)	258 (44.2)	261 (53.7)
6/5	7.92 s	7.33 s	3.90 (s, 3H)	2.58 (s, 3H)	153.5	143.8	105.2	150.7	162.2	55.6	20.1, 56.5	362 (8.7)	363 (7.0)	363sh (9.1)
		6.92 s	7.03 (d, 2H, J = 8.6 Hz)	3.83 (s, 3H)		122.6	157.8	107.5	157.2	114.9, 123.4	57.5	328 (16.1)	322 (12.6)	334 (15.5)
	[d]		7.32 (d, 2H, J = 8.6 Hz)	4.20 (s, 3H)	[d]					131.7, 160.1	120.2, 139.6	262 (64.7)	259 (48.8)	264 (47.0)
6/6	8.38 s	7.81 s	3.77 (s, 3H)	2.60 (s, 3H)	152.4	143.3	105.9	150.7	159.3	55.7, 55.9	19.8, 56.1	368 (7.1)	364 (9.3)	368 (7.9)
		7.01 s	3.78 (s, 3H)	3.85 (s, 3H)		122.4	156.7	107.4	156.7	111.4, 113.9	57.4	326 (15.1)	322 (14.2)	333 (15.2)
	[c]		7.17 (d, 1H, J = 8.3 Hz)	4.15 (s, 3H)	[c]					122.5, 123.9	121.1	261 (49.5)	258 (51.0)	261 (47.5)
			7.18-7.34 (m, 4H)							148.3, 150.7	138.7			
6/7	8.47 s	7.86 s	7.93 (d, 2H, J = 8.5 Hz)	2.63 (s, 3H)	154.0	143.8	106.1	152.9	162.9	123.7, 132.1	19.8, 56.4	353sh (7.8)	360 (5.0)	359sh (7.4)
		6.72 s	8.45 (d, 2H, J = 8.5 Hz)	3.74 (s, 3H)		123.5	159.6	106.4	154.0	135.5, 148.8	57.6	340 (16.8)	325 (9.4)	333 (14.9)
	[c]			4.17 (s, 3H)	[c]						122.3, 139.2	261 (49.1)	259 (35.5)	261 (46.1)
						122.3, 139.2261 (49.1)259 (35.5)				261 (46.1)				

[a] Taken in a mixture of deuteriochloroform and trifluoroacetic acid; [b] two peaks; [c] taken in DMSO-d_6; [d] taken in deuteriochloroform.

Table II

Synthetic and Analytical Data of the 5'-alkylthio-1,2,4-triazol-3'-yl-isoquinolinium Salts (**1**)

Com.	R	R^1 R^2	R^3	Yield %	Mp (°C) (cryst. from)	Lit. [2]	Molecular formula (MW)	Analysis % Calcd./Found C	H	N	S	F	Cl
1/1	4-Fluoro-phenyl	Methoxy Methoxy	Ethyl	53	169-171 (CH_3CN)	171-174 (CH_3CN)	$C_{22}H_{21}FN_4O_2S$ (424.50)	62.25 62.15	4.99 5.06	13.20 13.06	7.55 7.61	4.48 4.53	
1/2	4-Fluoro-phenyl	Methoxy Methoxy	2-Pro-pyl	56	168-170 (Dioxane)	166-168 (Dioxane) [a]	$C_{23}H_{23}FN_4O_2S$ (438.53)	63.00 62.88	5.29 5.37	12.78 12.85	7.31 7.23	4.33 4.29	
1/3	4-Chlo-rophenyl	Methoxy Methoxy	Methyl	56	157-160 (EtOH)	159-162 (EtOH)	$C_{21}H_{19}ClN_4O_2S$ (426.93)	59.08 58.92	4.49 4.55	13.12 13.28	7.51 7.44		8.30 8.23

[a] As a consequence of a typing error given in [2] as 208-210°.

Table IIa

Pmr and Cmr Spectral Data of 5'-Alkylthio-1,2,4-triazol-3'-yl-isoquinolinium Salts (**1**) Taken in Deuteriochloroform

Comp.	H-4	H-5 H-8	R	R^3	other	C-1	C-3 C-4	C-5 C-6	C-7 C-8	C-3' C-4'	R	R^3	other
1/1	8.40 s	7.76 s 6.77 s	7.17 (dd, 2H, J = 8.4, 8.6 Hz) 7.39 (dd, 2H, J = 4.9, 8.6 Hz)	1.23 (t, 3H, J = 7.3 Hz) 3.16 (q, 2H, J = 7.3 Hz)	2.52 (s, 3H) 3.81 (s, 3H) 4.25 (s, 3H)	155.4	144.8 123.2	105.9 159.2	153.0 106.2	154.8 156.5	116.0 (d, J = 22.1 Hz) 125.7 (d, J = 3.4 Hz) 132.3 (d, J = 8.8 Hz) 163.7 (d, J = 253.3 Hz)	14.9 27.6	20.4 56.3 58.1 122.8 138.8
1/2	8.45	7.82 s 6.76 s	7.16 (dd, 2H, J = 8.4, 8.7 Hz) 7.39 (dd, 2H, J = 5.0, 8.7 Hz)	1.23 (d, 6H, J = 6.7 Hz) 3.84 (qi, 1H, J = 6.7 Hz)	2.50 (s, 3H) 3.81 (s, 3H) 4.25 (s, 3H)	155.2	144.7 123.2	105.9 159.1	152.9 106.0	154.9 155.6	115.7 (d, J = 21.9 Hz) 125.7 (d, J = 3.8 Hz) 132.2 (d, J = 8.8 Hz) 163.6 (d, J = 253.3 Hz)	23.2 38.8	20.4 56.3 58.1 122.7 138.8
1/3	7.86 s	7.26 s 6.83 s	7.38 (d, 2H, J = 8.7 Hz) 7.42 (d, 2H, J = 8.7 Hz)	2.48 (s, 3H)	2.62 (s, 3H) 3.81 (s, 3H) 4.16 (s, 3H)	155.9	146.0 122.6	104.5 159.0	152.5 106.5	154.9 158.5	128.3 128.5 131.3 136.9	15.9	20.5 56.3 57.0 121.9 137.7

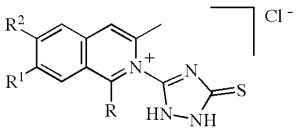
the analogy of the chemical shifts of the triazole carbon atoms 3' and 5' with those of the alkylthio derivatives **1** (Schemes 3 and 6).

Performing the reaction with 1,2-dibromoethane (**12**), 1,3-dibromopropane (**13**) and 1,4-dibromobutane (**14**) new type 5,6-dihydro-thiazolo[3,2-*b*][1,2,4]triazol-2-yl-isoquinolinium salts (**15**), 6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2-yl-isoquinolinium salts (**16**) and 5,6,7,8-tetrahydro[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2-yl-isoquinolinium salts (**17**), respectively, were obtained (Scheme 7).

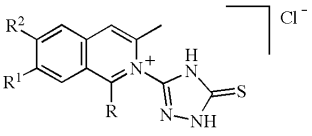
Their structure could again be deduced from mass spectra and the chemical shifts of the triazole carbon atoms. However, in this case the ring closure of the alkylene chain might also occur to the nitrogen atom 4' of the triazole moiety, thus isomeric structures **18**, **19** and **20**, respectively, had also to be taken in account (Scheme 8).

Structures **18-20** could be excluded by comparing the chemical shifts of the triazole carbon atoms of compounds **15-17** (Scheme 7) with those of the corresponding 1'-*N*-benzyl derivative **21** (Bn = benzyl, R = 4-methylphenyl, R^1, R^2 = methoxy), [2] (Scheme 9). In the case of the 2'- and 4'-*N*-benzyl isomers **22** (Bn = benzyl, R = 4-methyl-

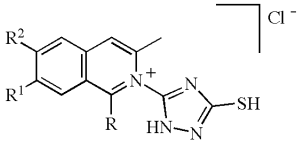
Scheme 4



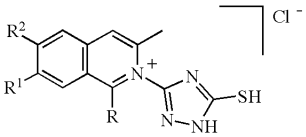
6a



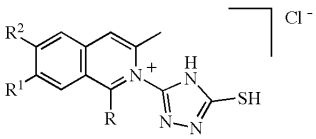
6b



6c

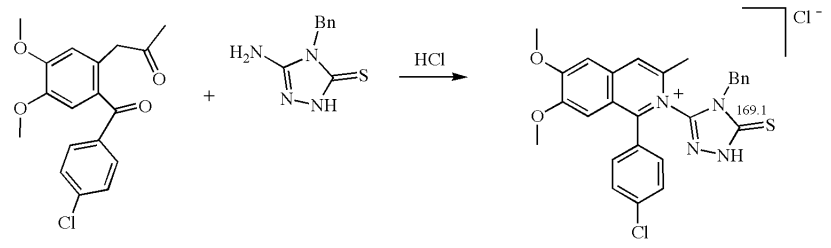


6d



6e

Scheme 5

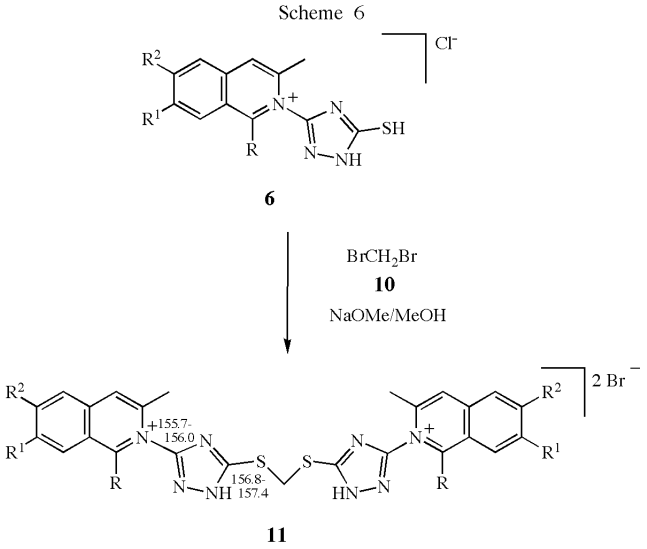


2, R = 4-chlorophenyl
R^1, R^2 = methoxy

8

9

Scheme 6



6

11

phenyl, R^1, R^2 = methoxy) and **23** (Bn = benzyl, R = 4-methylphenyl, R^1, R^2 = methoxy) [2] at least one of the triazole carbon atoms appeared at about 146 ppm.

Structures **15-17** were also proved through a preparative method, by the reactions of derivatives **2** with the corresponding 2-amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**24**), 2-amino-6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-*b*]-[1,3]thiazine (**25**) and 2-amino-5,6,7,8-tetrahydro[1,2,4]-triazolo[5,1-*b*][1,3]thiazepine (**26**), respectively (Scheme 10), which were recently prepared by us [1].

EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are not corrected. Infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The ms spectra were recorded on a Micromass LCT instrument in ES mode. The pmr and cmr measurements were performed using Varian Gemini-2000 and Varian Unity Inova instruments. Standard Varian HSQC and HMBC programs were used. As adsorbent of chromatographies Kieselgel 60 H (Merck 7736 for thin layer chromatography), as eluents different mixtures of petroleum ether, chloroform and methanol of continuously increasing polarities were used.

General Methods for the Synthesis of 5'-Mercapto-1'*H*-1,2,4-triazol-3'-yl-isoquinolinium Chlorides (**6**).

Method A.

A mixture of 15 mmole of the corresponding phenylacetone (**2**)[6], 15 mmole of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**5**) [3], 20 ml of acetonitrile, and 1 ml of concentrated hydrochloric acid was refluxed with stirring for 3 hours. The solution obtained crystallized. After cooling the crystals that precipitated were collected by filtration and washed with a small amount of acetonitrile to yield **6** (Table I, for the spectral data see Table Ia).

Method B

A mixture of 15 mmole of the corresponding pyrylium salt (**3**) [5], 15 mmole of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**5**)[3], 20 ml of acetonitrile, and 1 ml of concentrated hydrochloric acid was refluxed with stirring for 3 hours. After cooling the crystals that precipitated were collected by filtration and washed with a small amount of acetonitrile to yield **6** (Table I, for the spectral data see Table Ia).

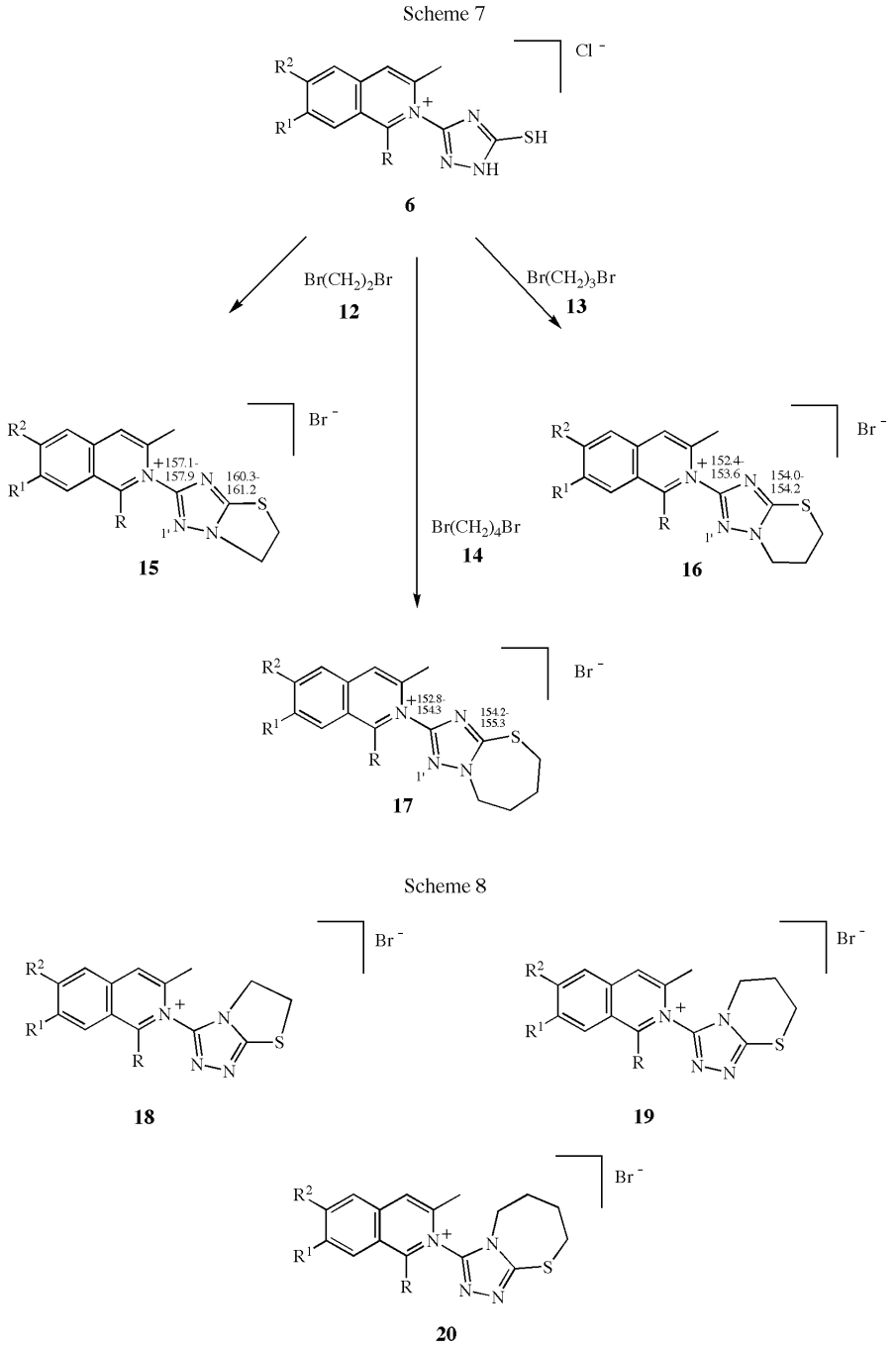
General Method for the *S*-alkylation of 5'-Mercapto-1'*H*-1,2,4-triazol-3'-yl-isoquinolinium Chlorides (**6**) to 5'-Alkylthio-1,2,4-triazol-3'-yl-isoquinolinium Zwitter Ions (**1**).

To a solution of 0.54 g (10 mmole) of sodium methoxide in 10 ml of methanol 5 mmole of the corresponding 5'-mercapto-1'*H*-1,2,4-triazol-3'-yl-isoquinolinium chloride (**6**) was added. To the red solution obtained 8 mmole of the corresponding alkyl iodide (R^3I) was added and stirred at room temperature for 48 hours. The methanol was evaporated *in vacuo* to dryness, to the residue 10 ml of water, 20 ml of 1 *M* sodium hydroxide and 50 ml of chloroform were added, the phases were separated, the water phase was extracted with 20 ml of chloroform, the combined chloroform phases were washed twice with 25 ml portions of water, dried over anhydrous sodium sulphate, and evaporated *in vacuo* to dryness. The crystalline residue obtained was recrystallized from an appropriate solvent to yield **1** (Table II, for the spectral data see Table IIa).

1-(4-Chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(4'-benzyl-4',5'-dihydro-1'*H*-1,2,4-triazole-5'-thione-3'-yl)isoquinolinium Chloride (**9**).

A mixture of 0.67 g (2 mmole) of 4,5-dimethoxy-2-(4-chlorobenzoyl)phenylacetone (**2**, R = 4-chlorophenyl, R^1, R^2 = methoxy) [6], 0.52 g (2.5 mmole) of 3-amino-4-benzyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**8**) [4], 5 ml of acetonitrile, and 0.5 ml of concentrated hydrochloric acid was refluxed with stirring for 5 hours. The solution obtained crystallised. After cooling

Scheme 7

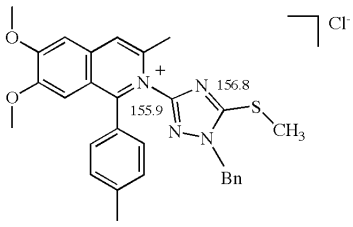


Scheme 8

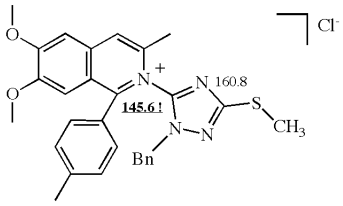
the crystals that precipitated were collected by filtration and washed with a small amount of acetonitrile to yield 0.96 g (89 %) of 1-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(4'-benzyl-4',5'-dihydro-1'*H*-1,2,4-triazol-5'-thione-3'-yl)isoquinolinium chloride (**9**), mp 238-241°; ms: (ES) m/z = 503 $[M]^+$; pmr (a mixture of deuteriochloroform and trifluoroacetic acid): δ 2.06 (s, 3H, CH_3-3), 3.84 (s, 3H, OCH_3-7), 4.25 (s, 3H, OCH_3-6), 4.55 [d (J = 15.0 Hz), 1H, $PhCH_2$-α_1)], 5.24 [d (J = 15.0 Hz), 1H, $PhCH_2$-α_2)], 6.79 (s, 1H, H-8), 6.86 [d (J = 7.6 Hz), 2H, PhH-3,5], 7.02 [dd (J = 2.1 and 8.2 Hz) 1H, BnH-4], 7.19 [d (J = 7.6 Hz), 2H, PhH-2,6), 7.21-7.58 (m, 4H, BnH), 7.59 (s, 1H, H-5), 8.07 (s, 1H, H-4); cmr (a mixture of deuteriochloroform and trifluoroacetic acid): δ 19.4 (CH_3-3), 48.2 ($BnCH_2$), 56.5 (OCH_3-6), 57.7 (OCH_3-7), 106.0 (C-5), 106.3 (C-8), 123.0 (C-8a), 123.3 (C-4), 125.1, 128.3, 129.5, 129.6, 130.0, 130.3, 130.7, 131.8, 132.5, 140.6 (ArC), 139.8 (C-4a), 143.8 (C-3), 154.2 (C-3'), 154.5 (C-7), 159.2 (C-6), 169.1 (C-5'); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 365.0 (6.0), 341.5 (10.9), 269.5 (29.4); uv (10 % EtOH + 90 % 0.1 M NaOH): λ_{max} ($\varepsilon.10^{-3}$) = 343.5 (3.45), 270 (7.0); uv (10 % EtOH + 90 % 0.1 M HCl): λ_{max} ($\varepsilon.10^{-3}$) = 369.5 (5.1), 341.5 (11.0), 268.0 (30.6).

Anal. Calcd. for $C_{27}H_{24}Cl_2N_4O_2S$ (MW 539.49): C, 60.11; H,

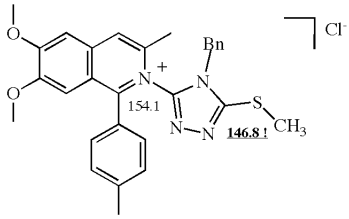
Scheme 9



21



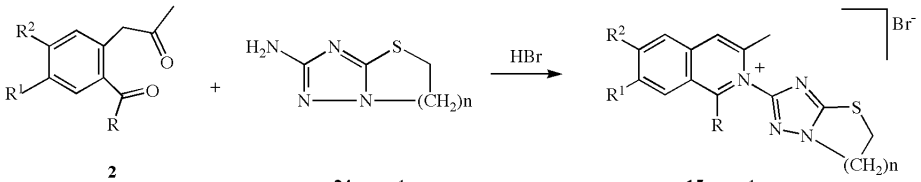
22



Bn = benzyl
R = 4-methylphenyl
R^1, R^2 = methoxy

23

Scheme 10



2

24: n = 1
25: n = 2
26: n = 3

15: n = 1
16: n = 2
17: n = 3

4.48; N, 10.39; S, 5.94; Cl, 13.14. Found: C, 59.84; H, 4.31; N, 10.52; S, 5.75; Cl, 12.81.

Bis-{3-[6,7-Dimethoxy-3-methyl-1-(4-methoxyphenyl)-isoquinolinium-2-yl]-1,2,4-triazole-5-ylthio}methane Dibromide (**11/1**).

To a solution of 0.97 g (18 mmole) of sodium methoxide in 10 ml of methanol 2.67 g (6 mmole) of 6,7-dimethoxy-3-methyl-1-(4-methoxyphenyl)-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/5**) and 2.09 g (12 mmole) of dibromomethane (**10**) were added. The reaction mixture was stirred at 40° for 5 hours then it was evaporated *in vacuo* to dryness. The residue was partitioned between 20 ml of water and 20 ml of chloroform, the phases were separated and the aqueous layer extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was crystallized from a mixture of 3 ml of ethanol and 12 ml of ethyl acetate. The crystals that precipitated were collected by filtration to yield 1.61 g (54 %) of bis-{3-[6,7-dimethoxy-3-methyl-1-(4-methoxyphenyl)-isoquinolinium-2-yl]-1,2,4-triazole-5-ylthio}methane dibromide (**11/1**), mp 213-216°; ms: (ES) m/z = 829 $[M^{2+}-H^+]^+$, 415 M^{2+}; pmr (deuteriochloroform): δ 2.52 (s, 6H, CH_3-3), 3.80 [s, 6H, OCH_3(p)], 3.82 (s, 6H, OCH_3-7), 4.23 (s, 6H, OCH_3-6), 4.62 (s, 2H, S-CH_2-S), 6.88 (s, 2H, H-8), 7.05 (bs, 4H, PhH-3,5), 7.30 (bs, 4H, PhH-2,6), 7.84 (s, 2H, H-5), 8.43 (s, 2H, H-4); pmr (DMSO-d_6): δ 2.50 [s, 6H, CH_3 (overlapped by DMSO)], 3.75 [s, 6H, OCH_3(p)], 3.78 (s, 6H, OCH_3-7), 4.15 (s, 6H, OCH_3-6), 4.84 (s, 2H, S-CH_2-S), 6.91 (s, 2H, H-8), 7.04 [d (J = 8.8 Hz), 4H, PhH-3,5], 7.44 [d (J = 8.8 Hz), 4H, PhH-2,6], 7.81 (s, 2H, H-5), 8.39 (s, 2H, H-4); cmr (deuteriochloroform): δ 20.4 (CH_3-3), 25.6 (S-CH_2-S), 55.8 [OCH_3(p)], 56.3 (OCH_3-6), 57.9 (OCH_3-7), 106.1 (C-8), 106.9 (C-5), 114.4 (PhC-3,5), 120.7* (C-8a), 120.9* (C-4), 122.9 (PhC-1), 131.6 (PhC-2,6), 138.9 (C-4a), 143.9 (C-3), 152.8 (C-7), 153.4 (C-1), 155.2 (C-3'), 157.2 (C-5'), 159.4 (C-6), 161.5 (PhC-4); cmr (DMSO-d_6): δ 19.9 (CH_3-3), 25.3 (S-CH_2-S), 55.5 [OCH_3(p)], 56.1 (OCH_3-6), 57.4 (OCH_3-7), 105.9 (C-8), 107.1 (C-5), 114.0 (PhC-3,5), 121.4 (C-8a), 122.5*(C-4), 122.6*(PhC-1), 132.0 (PhC-2,6), 138.5 (C-4a), 143.4 (C-3), 152.4 (C-7), 152.8 (C-1), 155.7 (C-3'), 156.8 (C-5'), 159.1 (C-6), 160.9 (PhC-4).

Anal. Calcd. for $C_{43}H_{42}Br_2N_8O_6S_2$ (MW 990.80): C, 52.13; H, 4.27; N, 11.31; S, 6.47; Br, 16.13. Found: C, 51.87; H, 4.16; N, 11.52; S, 6.66; Br, 15.95.

Bis-{3-[1-(4-Chlorophenyl)-6,7-dimethoxy-3-methyl-isoquinolinium-2-yl]-1,2,4-triazole-5-ylthio}methane Dibromide (**11/2**).

To a solution of 0.22 g (4 mmole) of sodium methoxide in 10 ml of methanol 0.90 g (2 mmole) of 6,7-dimethoxy-3-methyl-1-(4-chlorophenyl)-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/4**) and 0.70 g (4 mmole) of dibromomethane (**10**) were added. The reaction mixture was stirred at 40° for 5 hours and evaporated *in vacuo* to dryness. The residue

was partitioned between 20 ml of water and 20 ml of chloroform, the phases were separated and the aqueous layer extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was dry-column flash chromatographed. After evaporating the appropriate fractions *in vacuo* the residue was crystallized from 6 ml of 2-propanol, to yield 0.46 g (46%) of bis-{3-[1-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-isoquinolinium-2-yl]-1,2,4-triazole-5-ylthio}methane dibromide (**11/2**), mp 200-203°; ms: (ES) m/z = 837 $[M^{2+}-H^+]^+$, 419 M^{2+}; pmr (deuteriochloroform): δ 2.59 (s, 6H, CH_3-3), 3.80 (s, 6H, OCH_3-7), 4.16 (s, 6H, OCH_3-6), 4.48 (s, 2H, S-CH_2-S), 6.84 (s, 2H, H-8), 7.30 [d (J = 8.3 Hz), 4H, PhH-2,6], 7.34 (s, 2H, H-5), 7.39 [d (J = 8.3 Hz), 4H, PhH-3,5], 7.93 (s, 2H, H-4); cmr (deuteriochloroform): δ 20.5 (CH_3-3), 25.3 (S-CH_2-S), 56.3 (OCH_3-6), 57.1 (OCH_3-7), 104.9 (C-8), 106.5 (C-5), 122.1 (C-8a), 122.6 (C-4), 128.3 (PhC-1), 128.8 (PhC-3,5), 131.5 (PhC-2,6), 137.0 (PhC-4), 137.9 (C-4a), 146.1 (C-3), 152.6 (C-7), 155.1 (C-3'), 156.0 (C-1), 157.4 (C-5'), 158.5 (C-6).

Anal. Calcd. for $C_{41}H_{36}Br_2Cl_2N_8O_4S_2$ (MW 999.64): C, 49.26; H, 3.63; N, 11.21; S, 6.42; Br, 15.99, Cl, 7.09. Found: C, 49.31; H, 3.94; N, 11.42; S, 6.69; Br, 16.21; Cl, 6.99.

1-(4-Chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium Bromide (**15/1**).

To a solution of 0.22 g (4 mmole) of sodium methoxide in 10 ml of methanol 0.90 g (2 mmole) of 1-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/4**) and 0.75 g (4 mmole) of 1,2-dibromoethane (**12**) were added. The reaction mixture was stirred at 40° for 4 hours and evaporated *in vacuo* to dryness. The residue was partitioned between 15 ml of water and 15 ml of chloroform, the phases were separated and the aqueous layer extracted with 15 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was dry-column flash chromatographed. After evaporating the appropriate fractions *in vacuo* the residue was recrystallized from acetonitrile to yield 0.51 g (49 %) of 1-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium bromide (**15/1**) mp 220-224°; pmr (deuteriochloroform): δ 2.65 (s, 3H, CH_3-3), 3.81 (s, 3H, OCH_3-7), 4.18 [t (J = 6.6 Hz), 2H, CH_2-5'], 4.30 (s, 3H, OCH_3-6), 4.49 (bs, 2H, CH_2-6'), 6.70 (s, 1H, H-8), 7.36 [d (J = 8.3 Hz), 2H, PhH-3,5], 7.52 [d (J = 8.3 Hz), 2H, PhH-2,6), 8.32 (s, 1H, H-5), 8.97 (s, 1H, H-4); cmr (deuteriochloroform): δ 20.2 (CH_3-3), 33.7 (C-5'), 47.8 (C-6'), 56.3 (OCH_3-6), 58.4 (OCH_3-7), 105.5 (C-8), 107.1 (C-5), 122.5 (C-8a), 124.3 (C-4), 127.5 (PhC-1), 129.1 (PhC-3,5), 131.4 (PhC-2,6), 137.8 (PhC-4), 139.9 (C-4a), 143.8 (C-3), 153.3 (C-7), 154.3 (C-1), 157.9 (C-2'), 159.9 (C-6), 161.2 (C-3a').

Anal. Calcd. for $C_{22}H_{20}BrClN_4O_2S$ (MW 519.85): C, 50.83; H, 3.88; N, 10.78; S, 6.17; Br, 15.37; Cl, 6.82. Found: C, 50.67; H, 3.82; N, 10.58; S, 6.05; Br, 15.14; Cl, 6.75.

6,7-Dimethoxy-3-methyl-1-(4-methoxyphenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium Bromide (**15/2**).

To a solution of 0.97 g (18 mmole) of sodium methoxide in 10 ml of methanol 2.67 g (6 mmole) of 6,7-dimethoxy-3-methyl-1-(4-methoxyphenyl)-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/5**) and 2.25 g (12 mmole) of 1,2-dibromoethane (**12**) were added. The reaction mixture was stirred at 40° for 12 hours and evaporated *in vacuo* to dryness. The residue was partitioned between 20 ml of water and 20 ml of chloroform, the phases were separated and the aqueous layer extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was dry-column flash chromatographed. After evaporating the appropriate fractions *in vacuo* the residue was recrystallized from 25 ml of acetonitrile to yield 1.87 g (61 %) of 6,7-dimethoxy-3-methyl-1-(4-methoxyphenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium bromide (**15/2**) mp 194-198°; pmr (DMSO-d_6): δ 2.55 (s, 3H, CH_3-3), 3.74 (s, 3H, OCH_3-7), 3.84 [s, 3H, OCH_3(p)], 4.04 [t (J = 5.9 Hz), 2H, CH_2-5'], 4.14 (s, 3H, OCH_3-6), 4.40 [t (J = 5.9 Hz), 2H, CH_2-6'], 6.89 (s, 1H, H-8), 7.09 [d (J = 8.6 Hz), 2H, PhH-3,5], 7.46 [d (J = 8.7 Hz), 2H, PhH-2,6], 7.81 (s, 1H, H-5), 8.38 (s, 1H, H-4); cmr (deuteriochloroform): δ 19.9 (CH_3-3), 33.9 (C-5'), 47.4 (C-6'), 55.6 [OCH_3(p)], 56.1 (OCH_3-6), 57.5 (OCH_3-7), 105.9 (C-8), 107.1 (C-5), 114.0 (PhC-3,5), 121.2 (PhC-1), 122.5* (C-8a), 122.6* (C-4), 132.1 (PhC-2,6), 138.6 (C-4a), 143.4 (C-3), 152.4 (C-7), 156.8 (C-1), 157.9 (C-2'), 159.2 (C-6), 160.3 (PhC-4), 161.0 (C-3a').

Anal. Calcd. for $C_{23}H_{23}BrN_4O_3S$ (MW 515.43): C, 53.60; H, 4.50; N, 10.87; S, 6.22; Br, 15.50. Found: C, 53.44; H, 4.23; N, 10.68; S, 5.99; Br, 15.67.

6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium Bromide (**15/3**).

To a solution of 0.22 g (4 mmole) of sodium methoxide in 10 ml of methanol 0.92 g (2 mmole) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/7**) and 1.50 g (8 mmole) of 1,2-dibromoethane (**12**) were added. The reaction mixture was stirred at 40° for 36 hours and evaporated *in vacuo* to dryness. The residue was partitioned between 15 ml of water and 20 ml of chloroform, the phases were separated, the water layer extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was dry-column flash chromatographed. After evaporating the appropriate fractions the residue was crystallized from 6 ml of acetonitrile and collected by filtration to yield 0.48 g (45%) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)-isoquinolinium bromide (**15/3**), mp 230-235°; pmr (DMSO-d_6): δ 2.60 (s, 3H, CH_3-3), 3.73 (s, 3H, OCH_3-7), 4.00 [t (J = 7.5 Hz), 2H, CH_2-5'], 4.16 (s, 3H, OCH_3-6), 4.35 [t (J = 7.5 Hz), 2H, CH_2-6'], 6.74 (s, 1H, H-8), 7.83 [d (J = 8.5 Hz), 2H, PhH-2,6], 7.86 (s, 1H, H-5), 8.38 [d (J = 8.5 Hz), 2H, PhH-3,5), 8.47 (s, 1H, H-4); cmr (DMSO-d_6): δ 19.8 (CH_3-3), 33.9 (C-5'), 47.4 (C-6'), 56.4 (OCH_3-6), 57.5 (OCH_3-7), 105.9 (C-8), 106.4 (C-5), 122.2 (C-8a), 123.4 (C-4), 123.5 (PhC-3,5), 132.2 (PhC-2,6), 135.5 (PhC-1), 139.1 (C-4a), 143.6 (C-3), 148.8 (PhC-4), 152.8 (C-7), 154.0 (C-1), 157.1 (C-2'), 159.5 (C-6), 160.5 (C-3a').

Anal. Calcd. for $C_{22}H_{20}BrN_5O_4S$ (MW 530.40): C, 49.82; H, 3.80; N, 13.20; S, 6.05; Br, 15.06. Found: C, 49.64; H, 4.03; N, 13.31; S, 5.86; Br, 14.97.

6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium Bromide (**15/3**) – from **2** and **24**.

A mixture of 0.34 g (1 mmole) of 4,5-dimethoxy-2-(4-nitrobenzoyl)phenylacetone (**2** , R = 4-nitrophenyl) [6], 0.14 g (1

mmole) of 2-amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**24**) [1], 5 ml of acetonitrile and 0.3 ml of concentrated hydrobromic acid was refluxed with stirring for 20 hours. After cooling the crystals that precipitated were collected by filtration, washed with a small amount of acetonitrile and recrystallized from 5 ml of ethanol to yield 0.28 g (53%) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium bromide (**15/3**), mp 235-238°; identical (mixed mp, pmr) with that of **15/3** obtained in the previous experiment.

1-(4-Chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium Bromide (**16/1**).

To a solution of 0.54 g (10 mmole) of sodium methoxide in 20 ml of methanol 4.49 g (10 mmole) of the 1-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/4**) and 2.62 g (13 mmole) of 1,3-dibromopropane (**13**) were added. The reaction mixture was stirred at room temperature for 1 hour and it was evaporated *in vacuo* to dryness. The residue was partitioned between 20 ml of water and 30 ml of chloroform, the phases were separated, and the aqueous layer extracted with 30 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was crystallized from 15 ml of acetonitrile, collected by filtration and recrystallized from a mixture of 20 ml of acetonitrile and 2 ml of methanol to yield 2.39 g (45 %) of 1-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium bromide (**16/1**), mp 221-224°; pmr (deuteriochloroform): δ 2.27 (m, 2H, CH_2-6'), 2.68 (s, 3H, CH_3-3), 3.34 [t (J = 5.3 Hz), 2H, CH_2-5'], 3.80 (s, 3H, OCH_3-7), 4.27 [t (J = 5.3 Hz), CH_2, H-7'], 4.32 (s, 3H, OCH_3-6), 6.70 (s, 1H, H-8), 7.35 [d (J = 8.5 Hz), 2H, PhH-3,5], 7.51 [d (J = 8.5 Hz), 2H, PhH-2,6], 8.37 (s, 1H, H-5), 9.01 (s, 1H, H-4); cmr (deuteriochloroform): δ 20.3 (CH_3-3), 23.2 (C-6'), 26.1 (C-5'), 47.9 (C-7'), 56.3 (OCH_3-6), 58.5 (OCH_3-7), 105.5 (C-8), 107.3 (C-5), 122.5 (C-8a), 124.4 (C-4), 127.6 (PhC-1), 129.0 (PhC-3,5) 131.4 (PhC-2,6), 137.7 (PhC-4), 139.9 (C-4a), 143.8 (C-3), 151.0 (C-7), 153.3 (C-2'), 154.2* (C-3a'), 154.3* (C-1), 159.8 (C-6).

Anal. Calcd. for $C_{23}H_{22}BrClN_4O_2S$ (MW 533.88) C, 51.75 ; H, 4.15; N, 10.49; S, 6.01; Br, 14.97; Cl, 6.64. Found: C, 51.59; H, 4.18; N, 10.26; S, 6.00; Br, 14.83; Cl, 6.55.

6,7-Dimethoxy-3-methyl-1-(4-methoxyphenyl)-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium Bromide (**16/2**).

To a solution of 0.76 g (14 mmole) of sodium methoxide in 15 ml of methanol 2.67 g (6 mmole) of the 6,7-dimethoxy-3-methyl-1-(4-methoxy-phenyl)-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/5**) and 2.41 g (12 mmole) of 1,3-dibromopropane (**13**) were added. The reaction mixture was stirred at 40° for 4 hours and it was evaporated *in vacuo* to dryness. The residue was partitioned between 20 ml of water and 20 ml of chloroform, the phases were separated, the aqueous layer extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was crystallized from a mixture of 20 ml of ethyl acetate and 8 ml of acetonitrile to yield 2.25 g (71%) of 6,7-dimethoxy-3-methyl-1-(4-methoxyphenyl)-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium bromide (**16/2**) mp 197-200°; pmr (DMSO-d_6): δ 2.20 (m, 2H, CH_2-6'), 2.53 (s, 3H, CH_3-3), 3.36 (m, 2H, CH_2-5'), 3.74 (s, 3H, OCH_3-7), 3.84 [s, 3H, OCH_3(p)], 4.14 (s, 3H, OCH_3-6), 4.18 [t (J = 5.6 Hz), 2H, CH_2-7'], 6.89 (s, 1H, H-8), 7.08 [d (J = 8.5 Hz), 2H, PhH-3,5], 7.44 [d (J = 8.5 Hz), 2H, PhH-2,6], 7.81 (s, 1H, H-5), 8.38 (s, 1H, H-4); cmr (DMSO-d_6): δ 19.9 (CH_3-3), 23.1 (C-6'), 25.7 (C-5'), 47.5 (C-7'), 55.6 [OCH_3(p)], 56.1 (OCH_3-6), 57.4 (OCH_3-7), 105.9 (C-8), 107.1 (C-5), 113.9 (PhC-3,5), 121.2 (two peaks, PhC-1 and C-8a), 122.5 (C-4), 132.1 (PhC-2,6), 138.6 (C-4a), 143.3 (C-3), 150.1 (C-7), 152.4 (C-2'), 154.1 (C-3a'), 156.8 (C-1), 159.1 (C-6). 161.0 (PhC-4).

Anal. Calcd. for $C_{24}H_{25}BrN_4O_3S\cdot$ (MW 529.46) C, 54.45; H, 4.76; N, 10.58; S, 6.06; Br, 15.09. Found: C, 54.39; H, 4.68; N, 10.36; S, 6.22; Br, 14.83.

6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium Bromide (**16/3**).

To a solution of 0.22 g (4 mmole) of sodium methoxide in 10 ml of methanol 0.92 g (2 mmole) of the 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5'-mercapto-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium chloride (**6/7**) and 1.62 g (8 mmole) of 1,3-dibromopropane (**13**) were added. The reaction mixture was stirred at 60° for 40 hours and it was evaporated *in vacuo* to dryness. The residue was dissolved in a mixture of 10 ml of water, 5 ml of 0.1 *M* sodium hydroxide and 20 ml of chloroform, the phases were separated and the aqueous layer extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was crystallized from 10 ml of ethyl acetate to yield 0.56 g (51 %) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium bromide (**16/3**) mp 188-191°; pmr (DMSO-d_6): δ 2.23 (m, 2H, CH_2-6'), 2.59 (s, 3H, CH_3-3), 3.30 [t (J = 5.5 Hz), 2H, CH_2-5'], 3.74 (s, 3H, OCH_3-7), 4.12 [t (J = 5.7 Hz), 2H, CH_2-7'], 4.16 (s, 3H, OCH_3-6), 6.75 (s, 1H, H-8), 7.83 [d (J = 8.6 Hz), 2H, PhH-2,6], 7.88 (s, 1H, H-5), 8.38 [d (J = 8.6 Hz), 2H, PhH-3,5], 8.50 (s, 1H, H-4); cmr (DMSO-d_6): δ 19.9 (CH_3-3), 23.0 (C-6'), 25.7 (C-5'), 47.5 (C-7'), 56.4 (OCH_3-6), 57.6 (OCH_3-7), 106.0 (C-8), 106.4 (C-5), 122.3 (C-8a), 123.5 (two peaks, C-4 and PhC-3,5), 132.2 (PhC-2,6), 135.6 (PhC-1), 139.0 (C-4a), 143.6 (C-3), 148.8 (PhC-4), 150.4 (C-7), 152.8 (C-2'), 153.6 (C-1), 154.0 (C-3a'), 159.5 (C-6).

Anal. Calcd. for $C_{23}H_{22}BrN_5O_4S\cdot$ (MW 544.43) C, 50.74; H, 4.07; N, 12.86; S, 5.89; Br, 14.68. Found: C, 50.49; H, 4.08; N, 13.02; S, 5.93; Br, 14.57.

6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium Bromide (**16/3**) – from **2** and **25**.

A mixture of 0.34 g (1 mmole) of the 4,5-dimethoxy-2-(4-nitrobenzoyl)phenylacetone (**2**, R = 4-nitrophenyl) [6], 0.16 g (1 mmole) of 2-amino-6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-*b*]-[1,3]thiazine (**25**) [1], 5 ml of acetonitrile and 0.3 ml of concentrated hydrobromic acid was stirred at 70° for 6 hours. The reaction mixture was evaporated *in vacuo* to dryness and the residue crystallized from 4 ml of 2-propanol to yield 0.23 g (43 %) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2'-yl)isoquinolinium bromide

(**16/3**), mp 185-188°; identical (mixed mp, pmr) with that of **16/3** obtained in the previous experiment.

6,7-Dimethoxy-1-(4-fluorophenyl)-3-methyl-*N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2'-yl)isoquinolinium Bromide (**17/1**).

To a solution of 0.11 g (2 mmole) of sodium methoxide in 5 ml of methanol 0.43 g (1 mmole) of 6,7-dimethoxy-1-(4-fluorophenyl)-3-methyl-*N*-(2',3'-dihydro-1'*H*-1,2,4-triazole-3'-thione-5'-yl)isoquinolinium chloride (**6/3**) and 0.65 g (3 mmole) of 1,4-dibromobutane (**14**) were added. The reaction mixture was stirred at room temperature for 1 hour and evaporated *in vacuo* to dryness. The residue was dissolved in a mixture of 5 ml of water, 5 ml of 1.0 *M* sodium hydroxide and 10 ml of chloroform, the phases were separated, the aqueous layer was extracted with 10 ml of chloroform, the collected organic phases were washed with 5 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was dry-column flash chromatographed. After evaporating the solvents from the appropriate fractions *in vacuo*, the residue was crystallized from a mixture of 5 ml of ethyl acetate and 5 ml of acetonitrile to yield 0.19 g (36 %) of 6,7-dimethoxy-1-(4-fluorophenyl)-3-methyl-*N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2'-yl)-isoquinolinium bromide (**17/1**), mp 158-161°; pmr (deuteriochloroform): δ 1.77 (m, 2H, CH_2-6'), 2.23 (m, 2H, CH_2-7'), 2.67 (s, 3H, CH_3-3), 2.77 [t (J =5.5 Hz), 2H, CH_2-5'), 3.81 (s, 3H, OCH_3-7), 4.32 (s, 3H, OCH_3-6), 4.37 [t (J = 5.5 Hz), 2H, CH_2-8'], 6.72 (s, 1H, H-8), 7.25 [dd (J = 8.4 and 8.6 Hz), 2H, PhH-2,6], 7.43 [dd (J = 5.1 and 8.6 Hz), 2H, PhH-3,5], 8.33 (s, 1H, H-5), 9.02 (s, 1H, H-4); cmr (deuteriochloroform): δ 20.3 (CH_3-3), 26.1 (C-6'), 31.0 (C-7'), 32.6 (C-5'), 52.0 (C-8'), 56.3 (OCH_3-6), 58.5 (OCH_3-7), 105.5 (C-8), 107.5 (C-5), 115.9 [d (J = 22.1 Hz), PhC-3,5], 122.6 (C-8a), 124.6 (C-4), 125.7 [d (J = 3.4 Hz), PhC-1], 132.5 [d (J = 8.4 Hz), PhC-2,6], 140.0 (C-4a), 143.6 (C-3), 153.3 (C-7), 154.3* (C-2'), 154.6* (C-1), 155.3 (C-3a'), 159.9 (C-6), 163.7 [d (J = 253.6 Hz), PhC-4].

Anal. Calcd. for $C_{24}H_{24}BrFN_4O_2S$ (MW 531.45): C, 54.24; H, 4.55; N, 10.54; S, 6.03; Br, 15.04; F, 3.57. Found: C, 54.39; H, 4.78; N, 10.46; S, 6.00; Br, 14.83; F, 3.55.

6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6',7',8'-tetrahydro[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2'-yl)isoquinolinium Bromide (**17/2**).

To a solution of 0.22 g (4 mmole) of sodium methoxide in 10 ml of methanol 0.92 g (2 mmole) of the 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(2',3'-dihydro-1'*H*-1,2,4-triazole-3'-thione-5'-yl)isoquinolinium chloride (**6/7**) and 1.73 g (8 mmole) of 1,4-dibromobutane (**14**) were added. The reaction mixture was stirred at 60° for 40 hours and it was evaporated *in vacuo* to dryness. The residue was dissolved in a mixture of 10 ml of water, 5 ml of 1.0 *M* sodium hydroxide and 20 ml of chloroform, the phases were separated, the aqueous layer was extracted with 20 ml of chloroform. The collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was crystallized from a mixture of 9 ml of ethyl acetate and 1 ml of acetonitrile to yield 0.59 g (53 %) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2'-yl)isoquinolinium bromide (**17/2**), mp 175-178°; pmr (DMSO-d_6): δ 1.60 (m, 2H, CH_2-6'), 2.04 (m, 2H, CH_2-7'), 2.60 (s, 3H, CH_3-3), 2.84 (bs, 2H, CH_2-5'), 3.76 (s, 3H, OCH_3-7), 4.17 (s, 3H, OCH_3-6), 4.31 (bs, 2H, CH_2-8'), 6.81 (s, 1H, H-8), 7.84 [d (J = 8.7 Hz), 2H, PhH-2,6], 7.93 (s, 1H, H-5), 8.40 [d (J = 8.7 Hz), 2H, PhH-3,5), 8.54 (s, 1H, H-4); cmr (DMSO-d_6) δ 19.9 (CH_3-3), 25.6 (C-6'), 30.5 (C-7'), 32.1 (C-5'), 51.7 (C-8'), 56.4 (OCH_3-6), 57.6 (OCH_3-7), 106.1 (C-8), 106.4 (C-5), 122.2 (C-8a), 123.5 (two peaks C-4 and PhC-3,5), 132.2 (PhC-2,6), 135.8 (PhC-1), 139.1 (C-4a), 143.6 (C-3), 148.8 (PhC-4), 152.6 (C-7), 152.8 (C-2'), 154.1 (C-1), 154.2 (C-3a'), 159.5 (C-6).

Anal. Calcd. for $C_{24}H_{24}BrN_5O_4S\cdot$ (MW 558.46) C, 51.62; H, 4.33; N, 12.54; S, 5.74; Br, 14.31. Found: C, 51.59; H, 4.28; N, 10.46; S, 5.83; Br, 14.27.

6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2'-yl)isoquinolinium Bromide (**17/2**) – from **2** and **26**.

A mixture of 0.34 g (1 mmole) of the 4,5-dimethoxy-2-(4-nitrobenzoyl)phenylacetone (**2**, R = 4-nitrophenyl) [6], 0.25 g (2 mmole) of 3-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[5,1-*b*]-[1,3]thiazepine (**26**) [1], 5 ml of acetonitrile and 0.3 ml of concentrated hydrobromic acid was stirred at 70° for 6 hours. The reaction mixture was evaporated *in vacuo* to dryness. The residue was crystallized from a mixture of 10 ml of ethyl acetate and 3 ml of acetonitrile. The crystals that precipitated were collected by filtration and recrystallized from 4 ml ethanol to yield 0.19 g (34 %) of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2'-yl)isoquinolinium bromide (**17/2**), mp 176-179°; identical (mixed mp, pmr) with that of **17/2** obtained in the previous experiment.

Acknowledgement.

The authors wish to express their thanks to dr. Sándorné Sólyom for recording the ir spectra, to Miss Zsófia Kárpáti for recording the uv spectra, to dr. Éva Szabó and dr. Péter Slégel for recording the ms spectra, to Mrs. Magdolna Nagy and dr. István Kövesdi for recording the nmr spectra, to Mrs. Hirkóné Magdolna Csík for performing the elemental analyses and to Mrs. Lászlóné Berei for technical help.

REFERENCES AND NOTES

[1] For Part XLVIII see I. Prauda and J. Reiter, *J. Heterocyclic Chem.*, **40**, 821 (2003).

[2] I. Prauda, I. Kövesdi, P. Trinka and J. Reiter, *J. Heterocyclic Chem.*, **38**, 403 (2001).

[3] F. Arndt and E. Milde, *Chem. Ber.*, **54**, 2110 (1921).

[4] A. Orendt, J. Michl and J. Reiter, *Magn. Res. Chem*., **27**, 1 (1989).

[5] E. V. Kuznetsov, I. V. Shcherbakova and A. T. Balaban: "Benzo[*c*]Pyrylium Salts: Syntheses, Reactions, and Physical Properties" in *Advances in Heterocyclic Chemistry*, Vol. **50**, p. 160, Edited by A. R. Katritzky, Academic Press 1990

[6] F. Gatta, D. Piazza, M. R. del Giudice, M. Massotti, *Farmaco Ed. Sci.*, **40**, 942 (1985).