SYNTHESIS OF NEW SUBSTITUTED 3-MERCAPTO-1,2,4-TRIAZOLES POSSESSING 5-H-DIBENZO[*a,d*]CYCLOHEPTENE MOIETIES.

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ABSTRACT

Seven new thiosemicarbazides **2a-g** bearing 5H-dibenzo[*a,d*]cycloheptenyl-methyl group at N^1 and different alkyl or aryl substituents at N^4 were synthesized using classical procedures. ^{1}H-NMR analysis indicated the existence of two conformational isomers, a major axial (about 75%) and a minor equatorial one (25%) which are interconvertible by middle ring inversion. Cyclization of **2a-g** in NaOH solution afforded the corresponding 3-mercapto-1,2,4-triazoles **3a-g** which were separated as pure axial isomers. All the new compounds were extensively characterized by IR-, UV-, ^{1}H-NMR and ^{13}C-NMR spectroscopy and will be screened as carbonic anhydrase inhibitors in order to test the application of "bulky scaffold" strategy in this class of compounds.

INTRODUCTION

Continuing our investigations in the domain of biologically active compounds[1-4] we have shown recently[5] that aryl sulfonylureido-glycine hydroxamates containing a bulky 5H- dibenzo[*a,d*]cycloheptene moiety indicated a strong inhibition towards matrix metalloproteinases (MMP) and Clostridium histolyticum collagenase. In this preliminary paper we describe the synthesis and characterization of new 3-mercapto-1,2,4-triazoles containig the above-mentioned 5H-dibenzo[*a,d*]cycloheptene moiety. The new compounds will be biologically tested as carbonic anhydrase inhibitors (CAI) in order to see if the "bulky scaffold " strategy applied to MMP[5] could be expanded to CAI also.

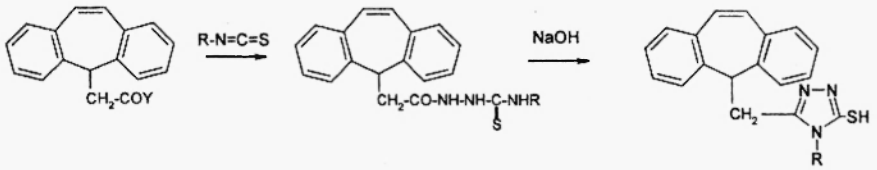
RESULTS

The synthesis of mercaptotriazoles **3a-g** was performed using the reaction sequence presented in Scheme 1.

The known ester **1b**[6] of the 5H-dibenzo[*a,d*]cycloheptenyl-acetic acid **1a**[7] was converted to the corresponding hydrazide **1c** (new compound, mp=161-163^{0}C; NMR δ values 8.7 and 9.3 ppm for NH and NH_2 protons; UV(MeOH+2%DMSO): 239nm and 291nm) on treatment with hydrazine hydrate in boiling ethanol (20hrs). Reaction of **1c** with alkyl- and aryl-isothiocyanates in anhydrous ethanol at reflux (6hrs) afforded the new thiosemicarbazides **2a-g** with yields varying between 76% and 97%. Treatment of **2a-g** with excess

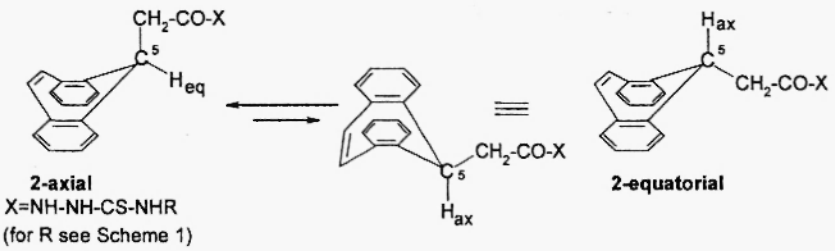
2N-NaOH solution at reflux (6hrs) produced the cyclization to the novel 3-mercapto-1,2,4-triazoles **3a-g** which were precipitated with acetic acid in yields around 70%).

Scheme 1



1a; Y=OH	**2**		**3**
1b; Y=OC_2H_5	m.p.(°C) 192-3	**a**; R=ethyl	m.p.(°C) 205-8(dec)
1c; Y=NH-NH_2	198-201	**b**; R=allyl	180-4
	148-50	**c**; R=n-butyl	316-19(dec)
	195-7	**d**; R=o-tolyl	230-2(dec)
	172-3	**e**; R=m-tolyl	215-7
	186-8	**f**; R=p-tolyl	231-3(dec)
	187-9	**g**; R=p-anisyl	256-8

The structures of thiosemicarbazides **2** were confirmed by their spectral data. Thus, in the IR spectra (FTS-135 BioRad apparatus; KBr) characteristic absorptions appear at 3110-3350 cm^{-1} (three bands; ν_{NH}); 1670-1690 cm^{-1} (ν_{CO}); along with all the frequencies characteristic for hydrocarbon moieties. All the compounds **2a-g** afford very similar UV spectra (MeOH+2%DMSO) exhibiting two major absorptions at 240-247 nm and 278-290.5nm. The ^{1}H-NMR spectra (VARIAN GEMINI 300MHz apparatus, d_6-DMSO) indicated the presence of two isomers, **2**-axial and **2**-equatorial in about 3:1 ratio (interconvertible by middle ring inversion).



In **2**-axial isomers the $H^{5'}$ (eq)* is deshielded, appearing as a triplet at 4.62-4.65ppm (J = 7.0-7.3Hz), whereas the $CH_2^{12'}$ protons shielded by the double bond show a doublet at 2.57-2.60ppm. A reversal of this situation occurs at **2**-equatorial isomers where the $H^{5'}$ (ax) appears as a shielded triplet at 3.73-3.76 ppm (J = 7.8-8.1Hz) and the $CH_2^{12'}$ protons as a doublet at 3.40-3.41ppm. The NH protons signals appear as singlets between 8.90-10.25ppm, the double bond protons $H^{10'}$ and $H^{11'}$as singlets at 7.03-7.21 whereas the aromatic protons occur in the usual interval (7.10-7.60ppm). The aliphatic side chains protons indicated also normal δ values. In the ^{13}C-NMR spectrum of **2a-g** (VARIAN GEMINI apparatus, 75MHz, d_6-DMSO) the dibenzo[*a,d*]cycloheptene moiety appears in a narrow δ domain (126-131ppm) with $C^{10'}$ and $C^{11'}$ easily recognizable at δ = 130.8ppm (A signal at δ ~181ppm could be attributed to C=S carbon atom).The remaining carbon atoms afford signals which partially overlap with those of the side chains. However the attributions of these signals could be made using incremental calculations for substituents and the results are very similar to those of mercaptotriazoles **3a-g** (see Table 2).

* For numbering of the skeleton see Tables 1 and 2

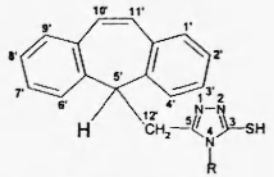


Table 1 ^{1}H-NMR data for mercaptotriazoles 3a-g (d_6-DMSO, δ ppm, J Hz)

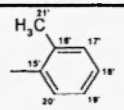
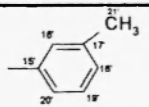
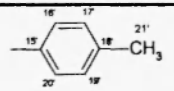
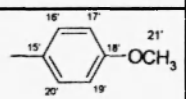
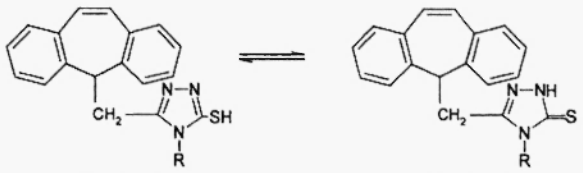
Nr.	R	$H^{1'-4'}$ $H^{6'-9'}$	$H^{5'}$	$H^{10'}$ $H^{11'}$	$H^{12'}$	$H^{15'}$	$H^{16'}$	$H^{17'}$	$H^{18'}$	$H^{19'}$	$H^{20'}$	$H^{21'}$	SH
3a	CH_2-CH_3	7.20-7.40 m	4.61 t (7.7)	7.01 s	3.09 d (7.7)	3.70 q (7.1)	1.09 t (7.1)	-	-	-	-	-	11.80
3b	CH_2-CH=CH_2	7.20-7.38 m	4.58 t (7.7)	7.00 s	3.08 d (7.7)	4.29ld (5.31)	5.70 ddt (17.3, 10.8 5.3)	4.22 ld(17.3) 5.16ld(10.3)	-	-	-	-	10.90
3c	CH_2-CH_2-CH_2-CH_3	7.15-7.36 m	4,57 t (7.7)	7.02 s	3.08 d (7.7)	3.59 t (7.7)	1.45 m	1.26 m	0.90t (7.3)	-	-	-	10.80
3d		7.18-7.46 m	4.51 t (7.8)	6.67 d(12.0) 6.60 d(12.0)	2.89 dd (5.2, 7.80) 2.78 dd (5.2, 7.8)	-	-	7.18-7.46 m	7.18-7.46 m	7.18-7.46 m	7.18-7.46 m	1.84 s	10.72
3e		7.10-7.40 m	4.38 t (7.9)	6.62 s	2.97 d (7.9)	-	7.10-7.40m	-	7.10-7.40 m	7.10-7.40 m	7.10-7.40 m	2.41 s	11.02
3f		7.10-7.31 m	4.37 t (7.9)	6.66 s	2.97 d (7.9)	-	7.10-7.31 m	6.79 d (8.1)	-	6.79 d (8.1)	7.10-7.31 m	2.47 s	10.80
3g		7.15-7.28 m	4.41 t (7.8)	6.67 s	2.94 d (7.8)	-	6 96 d (8.9)	6.77 d (8.9)	-	6.77 t (8.9)	6.96 d (8.9)	3.89 s	10.80

Table2 ^{13}C-NMR data for mercaptotriazoles 3 (d_6-DMSO, δ ppm, J Hz)

Nr	R	$C^{5'}$	$C^{12'}$	$C^{10'}$ $C^{11'}$	C^{5}	C^{3}	$C^{1'}$ $C^{9'}$	$C^{2'}$ $C^{8'}$	$C^{3'}$ $C^{7'}$	$C^{4'}$ $C^{6'}$	$C^{13'}$	$C^{16'}$	$C^{17'}$	$C^{18'}$	$C^{19'}$	$C^{20'}$	$C^{21'}$	$C^{9'a}$ $C^{11'a}$	$C^{4'a}$ $C^{6'a}$
3a	CH_2-CH_3	52.3	26.1	131.0	150.8	166.1	130.0	129.2	127.3	129.8	38.6	13.6	-	-	-	-	-	133.7	138.6
3b	CH_2-CH=CH_2	52.2	26.4	130.9	151.4	167.1	130.0	129.2	127.2	129.7	45.4	130.4	118.2	-	-	-	-	133.7	138.6
3c	CH_2-CH_2-CH_2-CH_3	52.2	26.2	131.0	151.2	166.9	130.0	128.3	127.2	129.5	43.5	30.2	19.9	13.6	-	-	-	133.7	138.6
3d		52.2	25.8	130.6	151.4	167.4	130.0	128.6	127.0	129.0	138.6	131.8	129.7	129.6	127.2	127.2	17.4	133.8	138.6
3e		52.8	26.0	130.6	151.5	167.9	129.9	129.0	127.0	129.5	139.6	128.5	132.9	129.7	129.4	125.0	21.13	133.8	138.5
3f		52.5	26.0	130.6	151.5	168.0	130.2	129.4	127.1	129.9	140.0	127.0	127.7	130.4	127.7	127.0	21.4	133.8	138.4
3g		52.4	25.8	130.5	151.0	167.8	129.7	128.7	126.7	129.1	138.5	129.3	114.5	160.0	114.5	129.3	55.4	133.7	138.5

The structures of the mercaptotriazoles **3** were also proved on the basis of their spectral data. The IR spectra proved the cyclization of **2** to **3** by the disappearance of ν_{CO} band. Moreover instead of three NH bands of **2**, compounds **3** show (in KBr) only two bands at 3110-3130 and 3380-3450 cm^{-1} characteristic for –NH-CS. It seems that in KBr the mercaptotriazoles **3** exists in the form of their thionic tautomers:



3-thiolic form **3**-thionic form

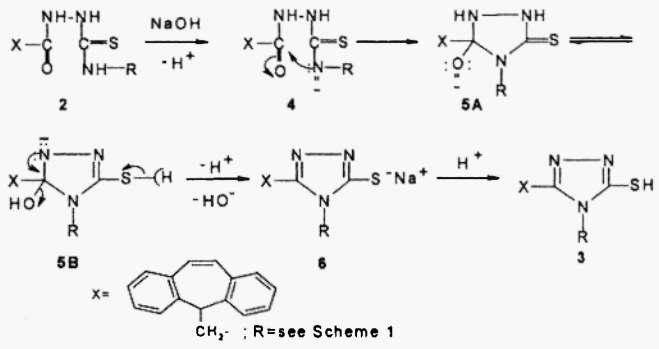
In the UV spectra (MeOH+2%DMSO) the triazoles **3a-g** indicated only two important absorption maxima: compounds **3a-c** at 255-256nm and 291-292nm and aromatic substituted compounds **3d-g** at 230-242nm and 262-267nm with a shoulder at about 287nm. The ^{1}H-NMR spectra of triazoles **3a-g** (Table 1) indicated the presence of a single conformational isomer, namely the axial one (corresponding to **2**-axial). The H^5 (eq) appears at δ =4.38-4.60ppm (triplet, J = 7.7Hz) and $CH_2^{12'}$ protons as a doublet at 3.10ppm in **3a-c** and at 2.80-2.95ppm in **3d-g**. Interestingly, in d_6-DMSO solution, the NH signals of **2a-g** totally disappeared being replaced by a singlet at δ =10.8-11.8ppm attributable to SH proton. Thus, in solution the above tautomeric equilibrium is shifted towards the thiolic form. A similar shift of the thione-thiole tautomerism was observed by us at mercaptotriazoles bearing phenazinic moieties[8]. Conversion of thiosemicarbazides **2** to mercaptotriazoles **3** is nicely supported also by ^{13}C-NMR spectra (Table 2) where a new quaternary carbon signal (for C^3) appears at δ =166-168ppm simultaneously with the disappearance of the C=S signal from **2** (δ =181ppm). Moreover, instead of C=O signal from **2** at 169-170ppm a new signal appears for C^5 of **3** at about 151ppm. The complete ^{1}H and ^{13}C-NMR data for **3a-g** are given in Tables 1,2.

DISCUSSION

Occurrence of thiosemicarbazides **2** in two conformational isomers, **2**-axial, **2**-equatorial, is not unexpected keeping in mind some previously reported results[9] when a similar slow conformational equilibrium was proved for 5-methyl-5H-dibenzo[*a,d*]cycloheptene and studied by variable temperature NMR.

Cyclization of thiosemicarbazides to mercaptotriazoles in alkaline medium could be explained as in other related cases[3] by the mechanism outlined in Scheme 2 having as essential intermediate the tautomeric anion **5**.

Scheme 2



X= ; R=see Scheme 1

To our surprise cyclizaton of **2** to **3** and the subsequent work-up were accompanied by the loss of minor equatorial isomer probably more soluble in acidic water. The resulting solid mercaptotriazoles **3** are pure axial isomers.

In conclusion, in this paper we described the synthesis and spectral characterization of seven new thiosemicarbazides and seven new mercaptotriazoles possesing the bulky 5H-dibenzo[*a,d*]cycloheptene moiety. The occurrence of thiosemicarbazides **2a-g** in two conformational isomeric forms was proved and a thiole-thione tautomeric equilibrium dependent on the physical state was observed for triazoles **3**. Compounds **3** will be biologically screened as CAI in order to see if the "bulky scaffold" strategy is applicable in this domain.

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