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A Straightforward Synthesis of Novel 4*H*-Thiazolo[3,2-*d*][1,5]benzodiazepine Derivatives

Regina Janciene, Ausra Vektariene, Zita Stumbreviciute, Lidija Kosychova, Algirdas Klimavicius, and Benedikta D. Puodziunaite

Department of Bioorganic Compounds Chemistry, Institute of Biochemistry, Mokslininku str. 12, LT-08662, Vilnius, Lithuania

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ABSTRACT: *The novel 4H-thiazolo[3,2-d][1,5]benzodiazepinium salts have been synthesized in a single step by the reaction of the variously substituted 2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1H)-thiones and bromoacetaldehyde diethyl acetal. Cyclization is obviously influenced by the nature of the substituents in the benzodiazepine system. Theoretical modeling and B3LYP DFT computational studies are presented.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:363–368, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20026

INTRODUCTION

Benzodiazepines and their annelated derivatives exhibit a wide spectrum of biological activities and have found applications in pharmaceutical chemistry [1]. More recently, considerable efforts have been devoted to discover new biologically active compounds in antitumor antibiotic group by the replacement of the pyrrole fused ring of pyrrolo[2,1-*c*][1,4]benzodiazepine system by thiazole moiety [2]. Moreover, a series of thiazolo[3,4-*a*]benzimidazole derivatives have been characterized as a new class of anti-HIV agents [3]. In numerous previous publications it has been described that adding another ring to the 1,4-benzodiazepine or 1,5-benzothiazepine moiety leads to an enhancement of the heptatomic ring mobility, meanwhile influencing the specific biological activity [4]. In connection with our investigations on the chemistry of *peri*-annelated imidazo[1,5]benzodiazepines with the in vitro anti-HIV activity [5] we have been interested in the synthesis of compounds containing an additional thiazole nucleus fused at 1 and 2 positions of 1,5-benzodiazepine system.

RESULTS AND DISCUSSION

In the present work we describe the synthesis of novel tricyclic title compounds obtained by one-step direct cyclofunctionalization of variously substituted tetrahydro-1,5-benzodiazepine-2-thiones with bidentate reagent (Scheme 1). The reaction of easily accessible compounds **1–11** with an excess of α-bromoacetaldehyde diethyl acetal in refluxing butan-2-one and water mixture gave the expected thiazolo[3,2-*d*][1,5]benzodiazepinium bromides **12–22** in relatively good yields (Table 1). In order to broaden the scope of this reaction we have employed the thiolactams which possess various functional substituents on the benzodiazepine skeleton.

Correspondence to: Regina Janciene; e-mail: apalaima@bchi.lt.
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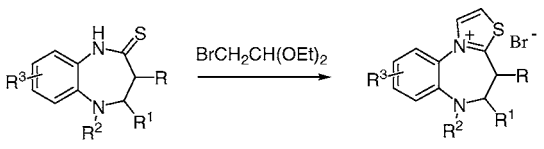

	R	R^1	R^2	R^3
1, 12	H	H	CHO	H
2, 13	Me	H	CHO	H
3, 14	H	Me	CHO	7-/8-NO_2
4, 15	H	Me	COMe	H
5, 16	H	H	CONHPh	H
6, 17	Me	H	CONHPh	H
7, 18	H	Me	CONHPh	H
8, 19	H	H	H	6,8-/7,9-Br_2
9, 20	Me	H	H	6,8-/7,9-Br_2
10, 21	H	Me	H	7-/8-NO_2
11, 22	Me	H	Me	H

SCHEME 1 Synthesis of 5,6-dihydro-4*H*-thiazolo[3,2-*d*][1,5]benzodiazepin-11-ium bromides.

Excess bidentate reagent was needed in this reaction. When this reaction was repeated using less of diethyl acetal (1.0 or 2.5 equiv), the cyclic thiolactam **1** was consumed slowly. However, after the addition of 5.0 equivalents of this reagent to the reaction mixture, the conversion of **1** was completed in 1 h. It is important to note that N_5-methylsubstituted thiolactam **11** (R^2 = Me) has been transformed into tricyclic derivative **22** just at the presence of the hydrobromic acid. This may be attributed to the different nucleophility of N_5 heterocyclic atom in the starting thiolactam **11** compared to N_5-acylated derivatives **1–7**. We assumed that protonation of the heterocyclic amine group would promote this reaction. Thus, using such approach thiolactam **11** was converted to **22** in 61% yield. Surprisingly, treatment of N_5-unsubstituted thiolactams **8–10** (R^2 = H) containing the bromine or nitro group at the aromatic ring under the neutral reaction conditions or at the presence of hydrobromic acid gave the corresponding products **19–21** in only 33% yield. Formation of the tricyclic system has been proved by ^{1}H NMR spectral data. In the spectra of compounds **12–22** the protons of the —CH=CH— group of the thiazole nucleus are observed as two doublets between 8.23 and 8.99 ppm. The ^{1}H NMR spectra of compounds **1–3** and **12–14** showed the existence of two forms exhibiting double sets of signals, due to the presence of rotational isomers of the exocyclic amide bond. New compounds were all characterized by IR, ^{1}H NMR (Table 2), and CHN analysis.

Thiolactams **1, 2, 4**, and **3** were obtained from the N_5-unsubstituted (R^2 = H) the corresponding

TABLE 1 Characterization of Compounds **1–22** and Elemental Analysis Data[a]

	Yield[b] (%)	*mp (°C)[c]*	*Molecular Formula (Molecular Weight)*	*Found (Calcd.)*		
				C	*H*	*N*
1	87	207–210	$C_{10}H_{10}N_2OS$ (206.27)	58.33 (58.23)	4.67 (4.89)	13.46 (13.58)
2	68	195–198	$C_{11}H_{12}N_2OS$ (220.29)	60.34 (59.98)	5.27 (5.49)	12.61 (12.72)
3	41	230–233	$C_{11}H_{11}N_3O_3S$ (265.29)	49.61 (49.80)	4.36 (4.18)	15.53 (15.84)
4	57	174–176	$C_{12}H_{14}N_2OS$ (234.32)	61.85 (61.51)	6.09 (6.02)	12.21 (11.95)
5	94	185–187	$C_{16}H_{15}N_3OS$ (297.38)	64.81 (64.62)	5.17 (5.08)	14.44 (14.13)
6	96	179–182	$C_{17}H_{17}N_3OS$ (311.41)	65.31 (65.57)	5.63 (5.50)	13.57 (13.49)
7	93	209–211	$C_{17}H_{17}N_3OS$ (311.41)	65.26 (65.57)	5.65 (5.50)	13.25 (13.49)
8	60	242–244	$C_9H_8Br_2N_2S$ (336.06)	32.02 (32.17)	2.56 (2.40)	8.72 (8.34)
9	70	203–205	$C_{10}H_{10}Br_2N_2S$ (350.09)	34.64 (34.31)	2.94 (2.88)	8.11 (8.00)
10	62	234–236	$C_{10}H_{11}N_3O_2S$ (237.28)	50.47 (50.62)	4.45 (4.67)	17.56 (17.71)
11	70	137–139[d]	–	–	–	–
12	73	236–238	$C_{12}H_{11}BrN_2OS$ (311.21)	46.24 (46.31)	3.62 (3.56)	8.70 (9.00)
13	81	222–224	$C_{13}H_{13}BrN_2OS$ (325.23)	48.12 (48.01)	4.06 (4.03)	8.57 (8.61)
14	45	>280 dec	$C_{13}H_{12}BrN_3O_3S$ (370.23)	42.26 (42.17)	3.19 (3.27)	11.33 (11.35)
15	91	253–256	$C_{14}H_{15}BrN_2OS$ (339.26)	49.41 (49.57)	4.37 (4.46)	8.19 (8.26)
16	60	232–234	$C_{18}H_{16}BrN_3OS$ (402.32)	53.62 (53.74)	4.22 (4.01)	10.48 (10.44)
17	85	190–193	$C_{19}H_{18}BrN_3OS$ (416.35)	54.73 (54.81)	4.49 (4.36)	10.36 (10.09)
18	81	181–183	$C_{19}H_{18}BrN_3OS$ (416.35)	54.93 (54.81)	4.48 (4.36)	10.11 (10.09)
19	34	>208 dec	$C_{11}H_9Br_3N_2S$ (441.00)	30.32 (29.96)	2.27 (2.06)	6.41 (6.35)
20	33	>107 dec	$C_{12}H_{11}Br_3N_2S$ (455.02)	31.57 (31.68)	2.69 (2.44)	5.89 (6.16)
21	31	>280	$C_{12}H_{12}Br_1N_3O_2S$ (342.22)	41.93 (42.12)	3.78 (3.53)	12.19 (12.28)
22·HBr	61	175–177[e]	$C_{13}H_{15}BrN_2S \cdot HBr \cdot 1.5\ CH_3OH$ (440.23)	39.83 (39.56)	4.80 (5.04)	6.27 (6.36)

[a]Satisfactory microanalyses were obtained: C ± 0.36; H ± 0.25; N ± 0.38.
[b]Yields of purified products.
[c]Crystallization solvent: **1–4** (EtOAc), **5–7, 10** (toluene), **8, 9** (*i*-PrOH).
[d]Lit. [6] 137–139°C (MeOH).
[e]Solvate with MeOH.

TABLE 2 Spectroscopic Data of Compounds **1–10** and **12–22**

	IR[a],ν (cm^{-1})	^1H *NMR* δ *(ppm), J (Hz)*
1[b]	1645, 3100, 3150	Two rotamers in a ratio of 86:14[c]. 2.99 (m, 2H, CH_2), 4.05 (m, 2H, CH_2N), 7.37 (m, 4H, arom), 8.22 (s, 1H, CHO), [8.41 (s, 1H, CHO)], [11.90 (s, 1H, NH)], 12.01 (s, 1H, NH)
2[b]	1640, 3100, 3150	Two rotamers in a ratio of 87:13[c]. 1.20 (d, 3H, CH_3), 3.04 (m, 1H, CH), 3.58 (dd, 1H, $J = 4.8, 12.8$, CH_2), 4.06 (dd, 1H, $J = 12.8$, CH_2), 7.38 (m, 4H, arom), 8.19 (s, 1H, CHO), [8.36 (s, 1H, CHO)], [11.90 (s, 1H, NH)], 12.02 (s, 1H, NH)
3[b]	1338, 1505, 1660, 3195	Two rotamers in a ratio of 85:15[c]. 1.19 (d, 3H, CH_3), [1.25 (d, 3H, CH_3)], 2.55–3.30 (m, 2H, CH_2), 4.95 (m, 1H, CH), 7.45 (d, 1H, $J = 8.8$, H-9), 8.16 (s, 1H, CHO), 8.20–8.50 (m, 2H, H-6, H-8), [8.51 (s, 1H, CHO)], 12.07 (s, 1H, NH)
4[d]	1665, 3190	1.19 (d, 3H, CH_3), 1.76 (s, 3H, CH_3CO), 2.60 (dd, 1H, $J = 12.8$, CH_2), 3.04 (dd, 1H, $J = 4.8, 12.8$, CH_2), 5.39 (m, 1H, CH), 6.80–7.65 (m, 4H, arom), 10.61 (s, 1H, NH)
5[d]	1660, 3155, 3290	3.00 (m, 2H, CH_2), 4.32 (m, 2H, CH_2N), 6.21 (s, 1H, NHCO), 6.90–7.50 (m, 9H, arom), 10.48 (s, 1H, NH)
6[d]	1645, 3155, 3290, 3370	1.26 (d, 3H, CH_3), 2.89 (m, 1H, CH), 3.75 (dd, 1H, $J = 5.6, 12.4$, CH_2), 4.39 (dd, 1H, $J = 12.4$, CH_2), 6.18 (s, 1H, NHCO), 6.80–7.55 (m, 9H, arom), 10.51 (s, 1H, NH)
7[d]	1655, 3150, 3310, 3415	1.26 (d, 3H, CH_3), 2.53 (dd, 1H, $J = 12.8$, CH_2), 3.05 (dd, 1H, $J = 4.8, 12.8$, CH_2), 5.29 (m, 1H, CH), 5.95 (s, 1H, NHCO), 6.80–7.70 (m, 9H, arom), 10.27 (s, 1H, NH)
8[b]	3120, 3340	3.00 (m, 2H, CH_2), 3.65 (m, 2H, CH_2N), 5.57 (s, 1H, NH), 7.30 (d, 1H, $J = 2.4$, H-9), 7.53 (d, 1H, $J = 2.4$, H-7), 11.65 (s, 1H, NHCS)
9[b]	3150, 3330	1.11 (d, 3H, CH_3), 2.80–3.70 (m, 3H, CH_2CH), 5.61 (s, 1H, NH), 7.30 (d, 1H, $J = 2.4$, H-9), 7.54 (d, 1H, $J = 2.4$, H-7), 11.75 (s, 1H, NHCS)
10[b]	1340, 1517, 3176, 3394	1.27 (d, 3H, CH_3), 2.67–3.17 (m, 2H, CH_2), 3.88 (m, 1H, CH), 6.33 (bs, 1H, NH), 7.22 (d, 1H, $J = 8.8$, H-9), 7.56 (dd, 1H, $J = 2.4, 8.8$, H-8), 7.81 (d, 1H, $J = 2.4$, H-6), 12.05 (bs, 1H, NHCS)
12[b]	1670	Two rotamers in a ratio of 82:18[c]. 3.71 (m, 2H, CH_2), 4.24 (m, 2H, CH_2N), [4.37 (m, 2H, CH_2N)], 7.50–8.00 (m, 4H, arom), 8.19 (s, 1H, CHO), [8.28 (s, 1H, CHO)], 8.43 (d, 1H, $J = 4.0$, HCS), [8.46 (d, 1H, $J = 4.0$, HCS)], 8.80 (d, 1H, $J = 4.0$, HCN), [8.86 (d, 1H, $J = 4.0$, HCN)]
13[b]	1680	Two rotamers in a ratio of 79:21[c]. [1.54 (d, 3H, CH_3)], 1.58 (d, 3H, CH_3), 3.40–4.00 (m, 2H, CH and CH_2), 4.31–4.62 (m, 1H, CH_2), 7.45–8.00 (m, 4H, arom), 8.18 (s, 1H, CHO), [8.26 (s, 1H, CHO)], 8.53 (d, 1H, $J = 4.0$, HCS), [8.57 (d, 1H, $J = 4.0$, HCS)], 8.86 (d, 1H, $J = 4.0$, HCN), [8.92 (d, 1H, $J = 4.0$, HCN)]
14[b]	1350, 1535, 1695	Two rotamers in a ratio of 80:20[c]. 1.29 (d, 3H, CH_3), [1.33 (d, 3H, CH_3)], 3.10 (dd, 1H, $J = 12.4, 14.8$, CH_2), 4.25 (dd, 1H, $J = 5.6, 14.4$, CH_2), 5.09 (m, 1H, CH), 8.12 (s, 1H, CHO), 8.23 (d, 1H, $J = 8.8$, H-10), [8.28 (d, 1H, $J = 8.8$, H-10)], [8.40 (s, 1H, CHO)], 8.47 (d, 1H, $J = 4.0$, HCS), [8.52 (d, 1H, $J = 4.0$, HCS)], 8.53–8.72 (m, 2H, H-7, H-9), 8.87 (d, 1H, $J = 4.0$, =HCN), [8.99 (d, 1H, $J = 4.0$, =HCN)]
15[e]	1655	1.34 (d, 3H, CH_3), 1.74 (s, 3H, CH_3CO), 2.87 (dd, 1H, $J = 12.0, 14.4$, CH_2), 4.02 (dd, 1H, $J = 5.6, 14.4$, CH_2), 5.39 (m, 1H, CH), 7.57–8.02 (m, 4H, arom), 8.35 (d, 1H, $J = 4.0$, HCS), 8.79 (d, 1H, $J = 4.0$, =HCN)
16[e]	1680, 3140, 3235	3.40–3.74 (m, 2H, CH_2), 4.10–4.60 (m, 2H, CH_2N), 6.85–7.35 and 7.60–7.90 (m, 9H, arom), 8.34 (d, 1H, $J = 4.0$, HCS), 8.67 (d, 1H, $J = 4.0$, HCN)
17[e]	1685, 3110, 3200, 3380	1.64 (d, 3H, CH_3), 3.58 (m, 1H, CH), 3.98–4.55 (m, 2H, CH_2N), 6.90–8.14 (m, 9H, arom), 8.39 (d, 1H, $J = 4.0$, HCS), 8.70 (d, 1H, $J = 4.0$, HCN)
18[e]	1670, 3110, 3235, 3410	1.41 (d, 3H, CH_3), 2.84 (dd, 1H, $J = 12.4, 14.8$, CH_2), 4.01 (dd, 1H, $J = 6.4, 14.8$, CH_2), 5.16 (m, 1H, CH), 6.84–7.34 and 7.55–8.04 (m, 9H, arom), 8.33 (d, 1H, $J = 4.0$, HCS), 8.67 (d, 1H, $J = 4.0$, =HCN)
19[b]	3105, 3280	3.67 (m, 2H, CH_2), 3.80 (m, 2H, CH_2N), 5.71 (s, 1H, NH), 7.92 (d, 1H, $J = 2.4$, H-8 or H-10), 8.09 (d, 1H, $J = 2.4$, H-10 or H-8), 8.34 (d, 1H, $J = 4.0$, HCS), 8.77 (d, 1H, $J = 4.0$, HCN)
20[e]	3127, 3410	1.61 (d, 3H, CH_3), 3.55–4.13 (m, 3H, CH_2 and CH), 7.91 (d, 1H, $J = 2.4$, H-8 or H-10), 8.01 (d, 1H, $J = 2.4$, H-10 or H-8), 8.30 (d, 1H, $J = 4.0$, HCS), 8.62 (d, 1H, $J = 4.0$, HCN)
21[e]	1349, 1532, 3272, 3412	1.39 (d, 3H, CH_3), 3.20–4.60 (m, 3H, CH_2 and CH), 7.80–8.20 (m, 3H, arom), 8.26 (d, 1H, $J = 4.0$, HCS), 8.66 (d, 1H, $J = 4.0$, =HCN)
22[e]**·HBr**	2257 (NH^+)	1.58 (d, 3H, CH_3), 2.84 (s, 3H, H_3CN), 3.30–3.90 (m, 3H, CH_2 and CH), 7.20–7.80 (m, 4H, arom), 8.30 (d, 1H, $J = 4.8$, HCS), 8.56 (d, 1H, $J = 4.0$, HCN)

[a]Compounds **1, 2, 4–9, 12–17** (nujol), **3, 10, 18–22** (KBr).
[b]Recorded in DMSO-d_6.
[c]^1H NMR peaks corresponding to the minor isomer of compounds **1–3** and **12–14** are given in square brackets.
[d]Recorded in $CDCl_3$.
[e]Recorded in CD_3OD.

3-R-4-R^1-2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1*H*)-thiones (**23**, R = R^1 = H; **24**, R = Me, R^1 = H; **25**, R = H, R^1 = Me) [6] and **10** [7] by formylation or acetylation according to the procedures previously described [8,9]. Treatment of **23–25** with phenylisocyanate resulted in the formation of carbamoylated derivatives **5–7**. Early described 4-methyl-7-nitro- and 6,8-dibromo-3-R(H or Me)-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-ones [8,9] were transformed into the corresponding thiolactams **10, 8, 9** by treatment with the phosphorous pentasulfide according to literature [7,10] procedure.

In order to get more insight into the nature of the studied cyclization process we investigated the situation by means of theoretical modeling. It is known that cyclic thioamides in the reaction mixture display the tautomeric equilibrium between the thione and thiol forms having a nucleophilic center either on the nitrogen atom or on the sulfur atom, respectively [7,11,12]. Moreover, the literature data show that in some cases of substitution of a thioamide moiety with various electrophilic reagents the sulfur atom attack is favored [12,13].

A convenient way to understand different reactivity of the variously substituted 2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1*H*)-thiones **1–11** is to examine the energetic parameters and the charge distribution of these species via quantum chemical calculations. The computations were performed using GAMESS 98 programme package [14]. Geometry optimizations of the starting materials and deprotonated forms were carried out in two steps. After initial geometry optimization using AM1 method the final optimizations were executed using DFT with the 6-31G basis set and the B3LYP method [14].

In order to estimate relative acidities at N_1-H and S-H positions of molecules **1–11** the proton affinities of the corresponding deprotonated tautomeric forms were determined. The close proton affinity values of deprotonated pairs (Table 3) clearly point to the corresponding neutral parent molecules having very similar acidity at these positions.

The charge distribution of the neutral molecules **1–11** and their deprotonated forms was determined by Lowdin population analysis. The computational results (Table 3) indicate that in thioamides the electron density on the N_1 nitrogen atom is slightly higher than that on the sulfur atom. On the other hand, deprotonation gives rise to a much larger increase in the electron density on the sulfur atom (∼0.2–0.3) relative to that in the neutral molecules. Moreover, a considerable increase of the negative charge is induced on the sulfur atom than that on N_1 nitrogen atom. Meanwhile, an interchange of the electron density on the N_5 nitrogen atom is negligible (data are not presented in Table). So, the negative charge in deprotonated form decrease in the following succession $S > N_1 > N_5$. Taking these charge distribution into account in both neutral and deprotonated form of the molecules it is possible that S-alkylation could take place as the primary step in the course of the cyclization. However, it is noteworthy that the substituents in aromatic ring (compounds **3, 8–10**) decrease the negative charge on the sulfur atom and simultaneously influence the coupling with the bidentate reactant to a great extent. Thus, theoretical computational studies are in agreement with the explanation of the preparative experiments.

Generally, we have described that the reaction of N_5-acylsubstituted 1,5-benzodiazepinethiones with

TABLE 3 Proton Affinity and Charge Distribution of **1–11**

	Proton Affinity (kJ/mol) and Position of Protonation		*Charge Distribution*			
			Neutral Molecule		*Deprotonated Form*	
	N_1	*S*	N_1	*S*	N_1	*S*
1	962.5	958.3	−0.233	−0.221	−0.308	−0.557
2	966.7	950.2	−0.240	−0.243	−0.285	−0.551
3	911.6	922.7	−0.258	−0.143	−0.294	−0.413
4	965.9	961.4	−0.232	−0.230	−0.302	−0.554
5	956.2	951.9	−0.234	−0.217	−0.307	−0.547
6	955.1	953.0	−0.231	−0.221	−0.300	−0.556
7	955.8	975.0	−0.233	−0.222	−0.301	−0.552
8	955.2	977.0	−0.233	−0.160	−0.310	−0.506
9	957.9	975.9	−0.231	−0.192	−0.292	−0.504
10	929.3	917.4	−0.250	−0.157	−0.292	−0.426
11	963.5	964.4	−0.242	−0.228	−0.308	−0.491

bromoacetaldehyde diethyl acetal provided an efficient method to prepare novel tricyclic thiazolo[3,2-*d*][1,5]benzodiazepines. When electron-donating methyl group was present at N_5 atom in thione precursor such compound could also be utilized by modifying experimental conditions to construct tricyclic system. These original derivatives are of potential interest in biologic evaluation.

EXPERIMENTAL

Melting points (uncorrected) were determined in open capillaries using a PTP (Thermopribor) apparatus. IR spectra were recorded on a Specord 75 IR or on a Spectrum BX FT-IR (Perkin-Elmer) spectrometer. ^{1}H NMR spectra were measured at 80 MHz on a BS 587A (Tesla) spectrometer with TMS as an internal reference. Elemental analyses were obtained on a Microelemental Analyzer (Labopribor). Ascending TLC was performed on Silufol UV_{254} silica gel plates with chloroform/ethyl acetate (14:7) as the eluent and were visualized with UV light and/or iodine vapor. Compound **11** was synthesized following the literature method [6].

*Synthesis of 4-R-5-R^1-6-R^2-5,6-dihydro-4H-thiazolo[3,2-d][1,5]benzodiazepin-11-ium bromides (**12–22**)*

General Procedure. To a stirred solution of the appropriate 1,5-benzodiazepine-2-thione derivative **1–10** (5.0 mmol) in butan-2-one (30–60 ml for **1, 2, 4–7** and 200 ml for **3, 8–10**) an excess of α-bromoacetaldehyde diethyl acetal (4.0 ml, 25.7 mmol) and water (0.5 ml) were added. The mixture was refluxed for 30 min and precipitation of product was observed. In each case the optimum reaction time (ca 0.5–1 h) was determined by TLC monitoring. Then the mixture was stored overnight in refrigerator and filtered. The crude products were recrystallized from anhydrous methanol/diethyl ether mixture.

When thiolactam **11** (5.0 mmol) was used, to its solution in butan-2-one (40 ml), an aqueous HBr (40%, 1.0 ml) was added instead of water. Subsequently diethyl acetal (4.0 ml) was added. After that the preparation of **22** had been performed according to the above procedure. Compound **22** was isolated as its hydrobromide. Thiazolobenzodiazepinium bromides **19–21** were also obtained from thiolactams **8–10** under the same reaction conditions.

*5-Formyl-3-R-4-R^1-2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1H)-thiones (**1–3**)*

Formylation of thiolactams **23, 24** [6], and **10** [7] with the mixture of 98% formic acid and acetic anhydride was conducted by using a general procedure [8].

*5-Acetyl-4-methyl-2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1H)-thione (**4**)*

Acetylation of thiolactam **25** (R = H, R^1 = Me) [6] with acetic anhydride and work up were conducted by using procedure [9].

*5-Phenylcarbamoyl-3-R-4-R^1-2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1H)-thiones (**5–7**)*

General Procedure. A mixture of the appropriate thiolactam **23–25** [6] (8.0 mmol) and phenylisocyanate (0.92 ml, 8.5 mmol) in anhydrous toluene (80 ml) was refluxed for 45 min. After cooling the mixture to room temperature the precipitated product was filtered and recrystallized from a suitable solvent.

Preparation of thiolactams **8–10**

Thionation of the corresponding lactams [8,9] was performed by treatment with the P_2S_5 in refluxing dry pyridine according to literature procedure [10].

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