Synthesis of Novel 1-Substituted [1,3]Thiazolo[3,2-*a*]-[1,5]benzodiazepine Derivatives From 1,5-Benzodiazepine-2-thiones and α-Halogen Carbonyl Compounds

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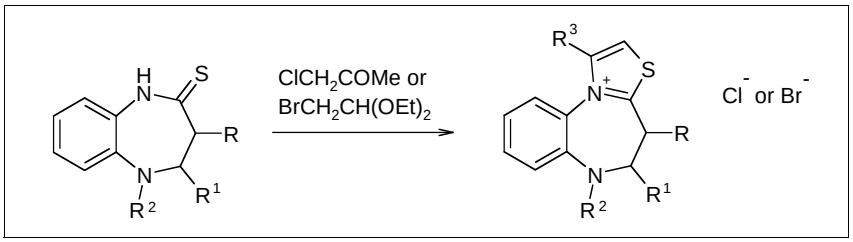

A number of substituted 4H,5H,6H-thiazolo[3,2-*a*][1,5]benzodiazepinium salts **2a-h, 5, 9**, which are based on the novel thiazolobenzodiazepine system, were prepared by condensation-cyclization of 1,5-benzodiazepine-2-thiones **1a-f, h, 4** with α-haloketones, as well as with α-bromoacetaldehyde diethyl acetal. The structure and stereochemistry of the ring system obtained were investigated by ^{1}H and ^{13}C nmr spectroscopy: the additional heterocyclic nucleus was found to appreciably influence the conformational mobility of the heptatomic ring. Upon treatment of salt **2d** with alkali the presence of the base enamine structure in solution has been postulated.

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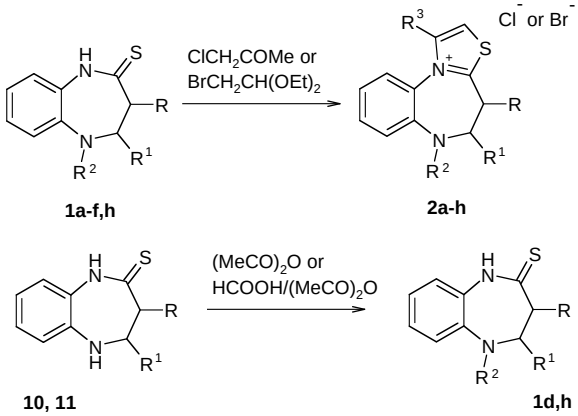
Introduction.

The 1,4- and 1,5-benzodiazepine bicycles derivatives are well known compounds, which are important in medicinal chemistry as therapeutic agents [1-4]. It is known from 1,4-benzodiazepine derivatives, that their pharmacological profile is enhanced by introducing various substituents into the benzodiazepine ring or by the annelation of another ring to this system [3-5]. As part of our studies towards the synthesis of new 1,5-benzodiazepine derivatives with possible pharmacological activity, and in connection with our interest in the chemistry of annelated ring systems, we here report the synthesis of novel thiazolobenzodiazepine derivatives. Usually, heteroannelated benzodiazepines are obtained by adding the additional ring onto an appropriate benzodiazepine derivative, for example a 2-thione [2,5].

Results and Discussion.

In the current work 1-methylsubstituted (R^3 = Me) thiazolobenzodiazepinium chlorides **2 a-f** were readily prepared by condensation of the thiolactams **1a-f** with an excess of chloroacetone in refluxing dry butan-2-one in relatively good yields (60-80 %) (Scheme 1). When this reaction was repeated in more polar anhydrous ethanol the

Scheme 1



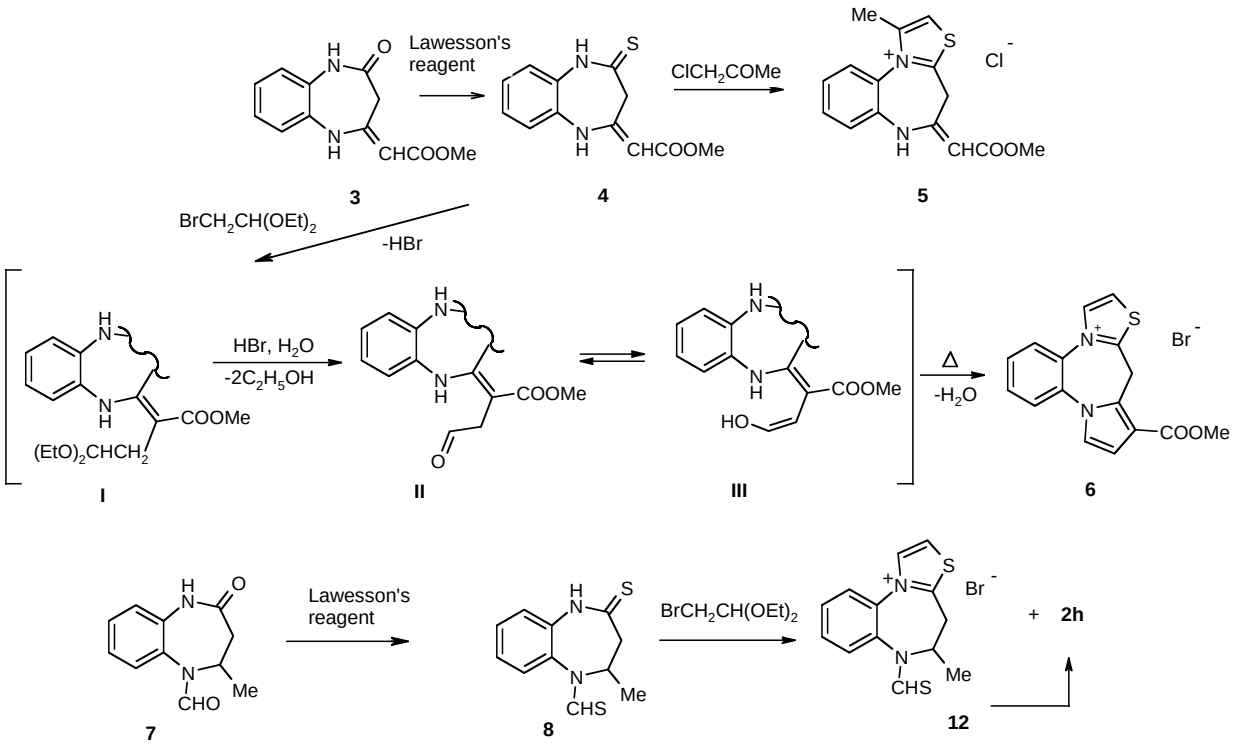
	R	R^1	R^2	R^3
1a, 2a	H	H	CONHPh	Me
1b, 2b	Me	H	CONHPh	Me
1c, 2c	H	Me	CONHPh	Me
1d, 2d	Me	H	COMe	Me
1e, 2e	H	Me	COMe	Me
1f, 2f	Me	H	CHO	Me
2g	Me	H	COMe	H
1h, 2h	H	Me	CHO	H
10	Me	H	COMe	-
11	H	Me	CHO	-

condensation reaction proceeded more quickly. However, the isolation of the reaction products under these conditions was rather complicated. For application of this cyclization methodology we have employed the thiolactams which possess various functional groups on the N_5 atom of the heterocyclic diazepine ring. Moreover, reaction of compounds **1d, h** with α-bromoacetaldehyde diethyl acetal gave the expected tricyclic derivatives (R^3 = H) as bromide salts **2g** and **2h**. The reaction proceeded more readily when using the acetal compared to chloroacetone which showed lower reactivity towards the thiolactams. This was evidenced by tlc analysis which indicated slow consumption of starting material. Synthesis of the starting materials **1a-c** and **1e-g** have been reported in [6]. Thiolactams **1d** and **1h** were obtained from N_5-unsubstituted (R^2 = H) corresponding 3-R-4-R^1-2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1*H*)-thiones (**10**, R = Me, R^1 = H; **11**, R = H, R^1 = Me) [7] by acetylation or formylation.

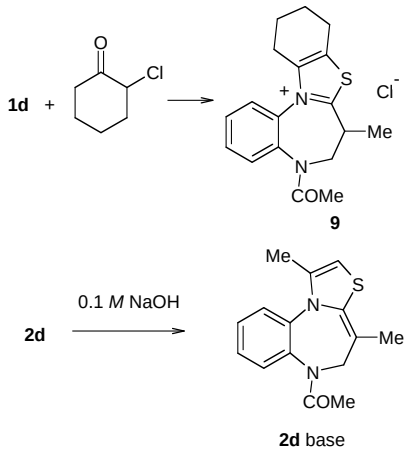
Attempts to prepare new tricyclic derivatives from the thiolactam **4** having in its structure an enamine fragment and ester group was not straightforward. Thionation of lactam **3** [8] with Lawesson's reagent in refluxing dry tetrahydrofuran lead to the desired thiolactam **4** (Scheme 2). However, the reaction of formylsubstituted lactam **7** [9] with the same reagent afforded product **8** in which both carbonyl groups experience the sulfurization. The cyclocondensation of compound **4** with chloroacetone lead to the formation of tricycle **5**. Reaction of **4** with an excess of α-bromoacetaldehyde diethyl acetal gave an unexpected tetracyclic derivative **6**. It is supposed that the alkylation of the nucleophilic =CH carbon atom (at the position 2 in **4**) with bromoacetal may occur. This allows to form bis-ethoxyalkyl intermediate **I** which in acidic media undergoes a hydrolysis to give intermediate **II** or **III** (enol form). The ring closure of **III** to the pyrrole derivative **6** takes place under heating by elimination of water. On the other hand, treatment of dithione **8** with bromoacetal gave the mixture of compounds **2h** and **12** in a 1:1 ratio. In this case desulfuration of the thioformyl group leading to the formation of the corresponding formylsubstituted tricyclic derivative **2h** under reaction conditions also took place. The structural identification by ^{1}H nmr spectroscopy of the mixture obtained indicates that compounds **2h** and **12** exist in the solution as a mixtures of *Z*- and *E*-isomers. Compound **12** was not isolated.

Our investigations revealed that employing the alicyclic α-haloketone for the one-step formation of the thiazolobenzodiazepine system required higher reaction temperature (Scheme 3). Thus, the reaction of **1d** with α-chlorocyclohexanone in refluxing dry dioxane afforded tricyclic compound **9** in 76 % yield. The treatment of chloride **2d** with an alkaline medium furnished the corresponding base which is unstable. Its formation at room temperature has been evidenced by nmr spectroscopy: addition of sodium hydroxide to a suspension of the chloride

Scheme 2



Scheme 3



2d in deuteriochloroform gave rise to ^{1}H nmr signals consistent with the presence of the thiazolobenzodiazepine as enamine **2d** (Table 2). The signals of the thiazole nucleus were shifted upfield at 5.60 ppm (CH) and 1.94 ppm (CH_3) with respect to those 8.61 ppm and 2.67 ppm respectively in the chloride **2d**. Further the 4-methyl group protons signals appear as doublet-doublets at 1.55 ppm (^{4}J = 1.2 Hz). All other resonance patterns agreed with the proposed structure, as well as ^{13}C nmr spectral data (Table 3).

and CH_3 signals (δ_H = 2.56-2.67 ppm) are particularly significant. It is interesting to note, that the spin patterns for the methylene protons of the seven-membered ring in compounds **2a, 5, 6** were significantly changed from those of precursors (**1a** and **4**). The AMNX spin system of the CH_2CH_2 moiety in compound **2a** ($\Delta\delta$ = 0.93 ppm for 4-CH_2 and $\Delta\delta$ = 0.76 ppm for 5-CH_2) indicates that the annelation of the thiazole nucleus to the "*a*" edge of the 1,5-benzodiazepine results in an increase of the ring inversion barrier of the heptatomic ring, while in thiolactam **1a** the protons of the ethylene fragment at room temperature form two groups of peaks as broadened triplet (3-CH_2) and broad singlet (4-CH_2). The methylene protons (A_2 system) of the bicyclic precursor **4** observed as singlet is changed into an AX spin system in tricyclic **5** and tetracyclic **6** derivatives and resonance as two doublets with $\Delta\delta$ = 0.8 ppm and $\Delta\delta$ =1.67 ppm respectively. Similar influence on the heptatomic ring reversal is consistent with the results obtained for ring-fused 1,4-benzodiazepines [10].

Two compounds **2a** and **2d** have been selected by National Cancer Institute (NCI) and evaluated in the preliminary screen of the *In Vitro* Anti-AIDS Drug Discovery Program for their suppression of HIV-induced cytopathogenicity. Unfortunately, IC_{50} (M) values 1.18×10^{-4} and $> 2.00\times10^{-4}$ for compounds **2a** and **2d**

Table 1

Physicochemical Properties of Compounds **1d,h** and **2a-h**

Compd.	Yield (%)	mp (°C)	Molecular Formula	Elemental Analysis Calcd./Found		
				C	H	N
1d	64	172-175 [a]	$C_{12}H_{14}N_2OS$	61.51	6.02	11.95
				61.44	6.20	11.71
1h	70	176-178 [a]	$C_{11}H_{12}N_2OS$	59.98	5.49	12.72
				60.19	5.36	12.61
2a	65	205-207	$C_{19}H_{18}ClN_3OS$	61.36	4.88	11.30
				61.14	4.97	11.27
2b	70	>199 dec	$C_{20}H_{20}ClN_3OS$	62.25	5.22	10.89
				62.39	5.03	10.96
2c	61	219-221	$C_{20}H_{20}ClN_3OS$	62.25	5.22	10.89
				62.37	5.11	10.73
2d	81	236-238	$C_{15}H_{17}ClN_2OS$	58.34	5.55	9.07
				58.27	5.61	9.01
2e	59	224-226	$C_{15}H_{17}ClN_2OS$	58.34	5.55	9.07
				58.45	5.49	9.16
2f	51	235-237	$C_{14}H_{15}ClN_2OS$	57.04	5.13	9.50
				57.21	5.01	9.43
2g	72	236-239	$C_{14}H_{15}BrN_2OS$	49.56	4.46	8.26
				49.51	4.38	8.39
2h	48	252-254	$C_{13}H_{13}BrN_2OS$	48.01	4.03	8.61
				48.27	3.94	8.77

[a] Recrystallization solvent – ethyl acetate.

New compounds were identified on the basis of analytical data, ir, ^{1}H and ^{13}C nmr spectra. In this connection the thiazole CH signals (δ_H = 7.91-8.61 ppm) respectively confirmed these derivatives to be inactive. Compounds **2c,e,f** have been tested in vitro for antitumour activity at the NCI [11]. Only the compound **2c** has been

scheduled for testing against the full panel of 60 human tumour cell lines. It proved to be the most effective tumour inhibitor at a concentration of 10^{-4} mol/l in renal cancer cell line 786-O and colon cancer cell line HCT-116.

Table 2

^{1}H NMR Chemical Shifts (δ) and IR Data for Compounds **1d,h** and **2a-h**

Compd.	^{1}H nmr (δ, ppm, J, Hz)	ir (ν, cm^{-1})
1d	1.29 (d, J = 6.6 Hz, 3H, 3-CH_3), 1.82 (s, 3H, CH_3CO), 2.93 (m, 1H, 3-H), 3.55 (dd, J = 5.5, 12.5 Hz, 1H, 4-H), 4.59 (dd, J= 12.5, 12.9 Hz, 1H, 4-H), 7.21 and 7.22 (dd, each, J = 1.4, 7.8 Hz, 2H, 6-H, 9-H), 7.33 and 7.42 (dt, each, J = 1.5, 7.8 Hz, 2H, 7-H, 8-H), 10.11 (br s, 1H, NH)	3170, 1640
1h	Two rotamers in a 9:1 ratio: 1.25 (d, J = 6.3 Hz, 3H, 2-CH_3), [1.33 (d, J = 6.5 Hz, 3H, 2-CH_3)], [2.79 (dd, J = 12.3, 12.6 Hz, 1H, 3-H)], 2.81 (dd, J = 12.8, 12.3 Hz, 1H, 3-H), 3.13 (dd, J= 4.6, 13.0 Hz, 1H, 3-H), [1H, 3-H, overlapped], [4.72 (m, 1H, 2-H)], 5.20 (m, 1H, 2-H), 7.18 and 7.24 (dd, each, 2H, 6-H, 9-H), 7.36 and 7.46 (ddd, each, 2H, 7-H, 8-H), 8.14 (s, 1H, CHO), [8.41 (s, 1H, CHO)], [10.24 (br s, 1H, NH)], 10.65 (br s, 1 H, NH).	3120, 1666
2a	2.62 (s, 3H, 1-CH_3), 2.99 (m, 1H, 4-H), 3.92 (m, 1H, 4-H), 3.95 (m, 1H, 5-H), 4.71 (m, 1H, 5-H), 7.10 (m, 1H, 4'-H), 7.20 (m, 2H, 3'-H, 5'-H), 7.33 (m, 2H, 2'-H, 6'-H), 7.64-7.75 (m, 4H, 7-, 8-, 9- and 10-H), 7.91 (s, 1H, 2-H).	3209, 1668
2b	1.56 (d, J = 6.6 Hz, 3H, 4-CH_3), 2.60 (s, 3H, 1-CH_3), 3.28 (m, 1H, 4-H), 3.89 (dd, J = 6.6, 12.1 Hz, 1H, 5-H), 4.35 (dd, J = 12.1, 11.9 Hz, 1H, 5-H), 6.94 (m, 1H, 4'-H), 7.17 (m, 2H, 3'-H, 5'-H), 7.27 (m, 2H, 2'-H, 6'-H), 7.59 (m, 1H, 7-H), 7.64 (m, 1H, 8-H), 7.68 (m, 1H, 9-H), 7.74 (m, 1H, 10-H), 7.96 (s, 1H, 2-H).	3209, 1683
2c	1.30 (d, J = 6.2 Hz, 3H, 5-CH_3), 2.56 (s, 3H, 1-CH_3), 2.58 (dd, J = 12.1, 14.81 Hz, 1H, 4-H), 3.82 (dd, J = 5.8, 14.8 Hz, 1H, 4-H), 5.18 (m, 1H, 5-H), 6.94 (m, 1H, 4'-H), 7.14 (m, 2H, 3'-H, 5'-H), 7.20 (m, 2H, 2'-H, 6'-H), 7.59 (m, 1H, 7-H), 7.66-7.76 (m, 3H, 8-, 9- and 10-H), 7.83 (s, 1H, 2-H).	3217, 3170, 1672
2d	1.64 (d, J = 6.6 Hz, 3H, 4-CH_3), 1.79 (s, 3H, CH_3CO), 2.67 (s, 3H, 1-CH_3), 3.48 (m, 1H, 4-H), 3.70 (dd, J = 6.6, 12.9 Hz, 1H, 5-H), 4.62 (dd, J = 12.5, 12.9 Hz, 1H, 5-H), 7.51 (dd, J = 1.4, 7.6 Hz, 1H, 7-H), 7.75 (dt, J = 1.4, 7.8 Hz, 1H, 8-H), 7.81 (dt, J = 1.2, 7.8 Hz, 1H, 9-H), 8.28 (dd, J = 1.2, 7.8 Hz, 1H, 10-H), 8.61 (s, 1H, 2-H).	1663
2d base	1.55 (dd, J = 1.2, 1.2 Hz, 3H, 4-CH_3), 1.89 (s, 3H, CH_3CO), 1.94 (d, J = 0.8 Hz, 3H, 1-CH_3), 3.50 (dq, J = 1.2, 16.5 Hz, 1H, 5-H), 5.22 (dq, J = 1.2, 16.5 Hz, 1H, 5-H), 5.60 (q, J = 0.8 Hz, 1H, 2-H), 6.99 and 7.25-7.41 (m, each, 4H, phenyl protons).	
2e	1.26 (d, J = 6.6 Hz, 3H, 5-CH_3), 1.70 (s, 3H, CH_3CO), 2.62 (s, 3H, 1-CH_3), 2.70 (dd, J = 12.9, 14.8 Hz, 1H, 4-H), 4.17 (dd, J = 5.1, 14.8 Hz, 1H, 4-H), 5.28 (m, 1H, 5-H), 7.40 (dd, J = 1.4, 7.8 Hz, 1H, 7-H), 7.72 (dt, J = 1.4, 7.8 Hz, 1H, 8-H), 7.78 (dt, J = 1.4, 7.8 Hz, 1H, 9-H), 8.17 (dd, J = 1.2, 7.8 Hz, 1H, 10-H), 8.51 (s, 1H, 2-H).	1662
2f	Two rotamers in a 86:14 ratio: 1.69 (d, J = 6.6 Hz, 3H, 4-CH_3), [2.56 (d, J = 1.0 Hz, 3H, 1-CH_3)], 2.60 (d, J = 1.2 Hz, 3H, 1-CH_3), [3.56-3.64 (m, 1H, 4-H)], 3.66 (m, 1H, 4-H), 3.81 (dd, J = 6.0, 12.6 Hz, 1H, 5-H), [4.12-4.32 (m, 2H, 5-H)], 4.38 (dd, J = 12.6, 12.7 Hz, 1H, 5-H), 7.50-8.00 (m, 4H, phenyl protons), [8.11 (q, J = 1.0 Hz, 1H, 2-H)], 8.14 (q, J = 1.0 Hz, 1H, 2-H), 8.26 (s, 1H, CHO)].	1672
2g	1.64 (d, J = 6.6 Hz, 3H, 4-CH_3), 1.75 (s, 3H, CH_3CO), 3.57 (m, 1H, 4-H), 3.78 (dd, J = 6.8, 12.9 Hz, 1H, 5-H), 4.74 (dd, J = 12.5, 12.9 Hz, 1H, 5-H), 7.45 (dd, J = 1.2, 7.8 Hz, 1H, 7-H), 7.69 (dt, J = 1.2, 7.8 Hz, 1H, 8-H), 7.75 (dt, J = 1.2, 7.8 Hz, 1H, 9-H), 8.11 (dd, J = 1.4, 7.8 Hz, 1H, 10-H), 8.54 (d, J = 3.9 Hz, 1H, 2-H), 8.76 (d, J = 3.9 Hz, 1H, 1-H).	1655
2h	Two rotamers in a 86:14 ratio: 1.40 (d, J = 6.3 Hz, 3H, 5-CH_3), [1.49 (d, J = 6.5 Hz, 3H, 5-CH_3)], [2.94 (dd, 1H, 4-CH_2)], 3.10 (dd, J = 12.6, 15.0 Hz, 1H, 4-H) 4.04 (dd, J = 4.8, 15.2 Hz, 1H, 4-H), [4.37 (dd, J = 5.0, 15.0 Hz, 1H, 4-H)], [5.1 (m, 1H, 5-H)], 5.29 (m, 1H, 5-H), 7.42-7.46, 7.77-7.86 and 8.04-8.08 (m, each, 4H, phenyl protons), 8.11 (s, 1H, CHO), [8.33 (s, 1H, CHO)], 8.38 (d, J = 4.0 Hz, 2-H), 8.59 (d, J = 4.0 Hz, 1H, 1-H).	1669, 1683

EXPERIMENTAL

Melting points were determined by the capillary method on a PTP apparatus and are uncorrected. The ir spectra (potassium bromide) were taken on a Perkin Elmer Spectrum GX FT-IR spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian-Mercury-vx-spectrometer at 400 MHz and Varian Unity Inova 300 spectrometer (300 MHz) in deuteriochloroform (compounds **1d,h, 2a-e** and **2g**) or in solvent systems: deuteriochloroform/deuteriomethanol 9:1 and 4:1 (compounds **2f** and **2h** respectively) (Tables 2, 3). The chemical shifts are referenced to tetramethylsilane (δ (^{1}H) = 0) and the solvent signal deuteriochloroform (δ (^{13}C) = 77.0 ppm), deuteriomethanol (δ (^{13}C) = 49.0 ppm) and hexadeuteriodimethylsulfoxide (δ (^{13}C) = 39.5 ppm). Nmr peaks corresponding to the minor isomer of compounds **1h, 2f, 2h** and **8** are given in square brackets. The CH_3, CH_2, CH and C_{quart} groups in ^{13}C nmr were differentiated by means of the APT or DEPT methods. Elemental analysis for C, H, N was performed on the Microelemental Analyzer (Labopribor). Elemental analysis data of all new compounds agree with the theoretical values to within 0.4%. Analytical tlc was carried out on Merck precoated silica gel aluminium rolls (60 F_{254}) with chloroform-ethyl acetate (2:1) as the eluent and the location of spots was detected by illumination with a uv lamp.

The compound (**3**) was obtained by literature procedure from *ortho*-phenylenediamine and dimethyl 1,3-acetonedicarboxylate [8].

General Procedure for the Synthesis of the 1-R^3-4-R-5-R^1-6-R^2-4*H*,5*H*,6*H*-Thiazolo[3,2-*a*][1,5]benzodiazepin-11-ium Chlorides (**2a-f**).

To a stirred solution of the appropriate 1,5-benzodiazepine-2-thione derivative **1a-f** (5.0 mmoles) in 75 ml of dry butan-2-one an excess of chloroacetone (4 ml, 50 mmoles) were added. The mixture was heated at reflux for 4-6 hours. In each case the optimum reaction time was determined by tlc monitoring. Then the reaction mixture was allowed to stand overnight in a

Table 3

^{13}C NMR data of compounds **1d,h** and **2a-h**

Compd.	^{13}C nmr (δ, ppm, J, Hz)
1d	16.84 (3-CH_3), 22.97 (5-CH_3), 40.65 (3-C), 57.78 (4-C), 122.64 (CH), 127.59 (CH), 129.26 (CH), 129.34 (CH), 135.02 (C), 135.33 (C), 170.08 (5-CO), 209.11 (2-C).
1h	Two rotamers a 9:1 ratio: 19.10 (2-CH_3), [22.13 (2-CH_3)], 48.21 (3-C), [48.51 (3-C)], 56.20 (2-C), [59.60 (2-C)], 122.39 (CH), [122.57 (CH)], [127.56 (CH)], 128.94 (CH), 129.45 (CH), [131.07], 131.30 (C), [135.75], 136.09 (C), [162.09 (CHO)], 162.12 (CHO), [202.59 (4-C)], 203.34 (4-C)
2a	14.95 (1-CH_3), 28.09 (4-C), 52.96 (5-C), 119.79 (CH), 120.52 (2',6'-C), 123.53 (CH), 126.26 (CH), 128.40 (3',5'-C), 129.33 (CH), 130.73 (CH), 132.23 (C), 132.81 (CH), 135.57 (C), 137.90 (1'-C), 145.86 (1-C), 154.83 (CO), 171.73 (3a-C).
2b	14.48 (CH_3), 14.93 (CH_3), 35.09 (4-C), 59.52 (5-C), 119.19 (CH), 120.41 (2',6'-C), 123.55 (CH), 126.70 (CH), 128.41 (3',5'-C), 129.59 (CH), 130.19 (CH), 132.26 (C), 132.91 (CH), 135.67 (C), 137.81 (1'-C), 146.58 (1-C), 154.58 (CO), 177.70 (3a-C).
2c	14.92 (1-CH_3), 18.97 (5-CH_3), 35.16 (4-C), 59.60 (5-C), 119.55 (CH), 120.85 (2',6'-C), 123.81 (CH), 126.73 (CH), 128.48 (3',5'-C), 130.14 (CH), 132.40 (CH), 132.72 (CH), 132.82 (C), 133.11 (C), 137.71 (1'-C), 145.85 (1-C), 153.79 (CO), 171.43 (3a-C).
2d	14.72 (CH_3), 15.39 (CH_3), 22.54 (6-CH_3), 34.90 (4-C), 57.41 (5-C), 122.04 (CH), 128.14 (CH), 129.85 (CH), 130.73 (CH), 132.01 (C), 132.75 (CH), 135.28 (C), 144.93 (1-C), 169.06 (6-CO), 177.60 (3a-C).
2d base	15.19 (1-CH_3), 19.09 (4-CH_3), 22.05 (6-CH_3), 49.75 (5-C), 98.27 (C), 100.47 (CH), 124.08 (CH), 126.04 (CH), 128.37 (CH), 128.49 (CH), 129.30 (C), 133.96 (C), 138.30 (C), 141.42 (C), 169.97 (CO).
2e	15.48 (1-CH_3), 18.70 (5-CH_3), 23.01 (6-CH_3), 34.97 (4-C), 58.36 (5-C), 122.59 (CH), 127.91 (CH), 130.70 (CH), 131.42 (CH), 132.41 (CH), 132.46 (C), 133.35 (C), 144.10 (1-C), 168.50 (6-CO), 171.56 (3a-C).
2f	Two rotamers in a 86:14 ratio: [14.08 (CH_3)], 14.59 (CH_3), [14.93 (CH_3)], 15.30 (CH_3), 33.94 (4-C), [35.08 (4-C)], 56.37 (5-C), [59.20 (5-C)], 120.13 (CH), [120.33 (CH)], [126.82 (CH)], 127.80 (CH), 129.29 (CH), 130.59 (CH), [130.81], 131.59 (C), [133.06 (C)], 133.42 (CH), 133.71 (C), [145.35(1-C)], 146.65 (1-C), 162.09 (6-C), [162.83 (6-C)], 178.23 (3a-C).
2g	15.30 (4-CH_3), 22.65 (6-CH_3), 34.55 (4-C), 57.66 (5-C), 125.41 (CH), 126.54 (CH), 129.97 (CH), 131.13 (CH), 132.59 (CH), 133.34 (CH), 134.22 (C), 136.95 (1-C), 170.06 (6-CO), 176.72 (3a-C).
2h	18.70 (5-CH_3), 33.35 (4-C), 57.65 (5-C), 125.02 (CH), 126.06 (CH), 130.16 (CH), 130.82 (C), 131.19 (CH), 133.00 (CH), 133.77 (C), 136.76 (CH), 161.86 (6-C), 170.38 (3a-C).

refrigerator. The resulting precipitate was collected and recrystallized from anhydrous methanol and diethyl ether mixture to yield the thiazolobenzodiazepine salts. Physicochemical properties of compounds are summarized in Tables 1, 2, 3.

General Procedure for the Synthesis of the 4-R-5-R^1-6-R^2-4*H*,5*H*,6*H*-Thiazolo[3,2-*a*][1,5]benzodiazepin-11-ium Bromides (**2g,h**).

Compounds **2g** and **2h** have been prepared from thiolactams **1d** and **1h** (5.0 mmoles) by treatment with α-bromoacetaldehyde diethyl acetal (4 ml, 25.7 mmoles) in 60 ml of refluxing butan-2-one and water (0.5 ml) mixture following the method previously described by us [6] (Tables 1, 2, 3).

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

A mixture of 2.04 g (10 mmoles) of thiolactam **10** [7] in 60 ml of dry chloroform and acetic anhydride (1.5 ml, 15 mmoles) was refluxed for 6 hours. After cooling the organic solution was washed with 0.1 *M* hydrochloric acid solution (2×20 ml), 5% aqueous sodium hydrogencarbonate solution (40 ml) and water, dried over magnesium sulfate and concentrated. A solid residue was purified by recrystallization to give 1.6 g of **1d** (Tables 1, 2, 3).

2-Methyl-4-thioxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbaldehyde (**1h**).

A mixture of 31 ml (30 mmoles) of acetic anhydride and 1.31 ml (30 mmoles) of 99.7% formic acid was heated at 50 °C for 2 hours. After this 5.7 g (30 mmoles) of thiolactam **11** [7] in 60 ml of dry chloroform was added and the reaction mixture was kept at room temperature for 12 hours. The reaction mixture was concentrated *in vacuo* and the solid residue was purified by recrystallization to give 4.6 g of **1h** (Tables 1, 2, 3).

Methyl (4-Thioxo-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ylidene)acetate (**4**).

To a warm solution of 1.01 g (2.5 mmoles) of Lawesson's reagent in 70 ml of dry tetrahydrofuran, 1.16 g (5.0 mmoles) of lactam **3** [8] was added and the reaction mixture was refluxed under stirring for 2 hours. After cooling to ambient temperature obtained precipitate was separated by filtration and purified by crystallization from dioxane to give 0.7 g (56%) of **4**, mp 233-235 °C; ir: 3437, 3257, 3164, 1663 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.56 (s, 2H, 3-H), 3.63 (s, 3H, OCH_3), 4.81 (s, 1H, 2-CHCO), 7.14-7.33 (m, 4H, phenyl protons), 10.28 (br s, 1H, NH), 12.34 (br s, 1H, NHCS); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 49.32 (CH_2), 50.39 (CH_3), 84.73 (CH), 122.58 (CH), 122.77 (CH), 124.30 (CH), 126.64 (CH), 130.54 (C), 132.26 (C), 155.29 (C), 169.61 (CO), 197.33 (4-C) ppm.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.27; H, 4.79; N, 11.13.

5-(2-Methoxy-2-oxoethylidene)-1-methyl-5,6-dihydro-4*H*-[1,3]-thiazolo[3,2-*a*][1,5]benzodiazepin-11-ium Chloride (**5**).

This compound was obtained according to the general procedure from **4** (1.2 g, 5.0 mmoles) and chloroacetone (4 ml, 50 mmoles) in 100 ml of dry butan-2-one and the reaction mixture was refluxed for 18 hours. The work up of the mixture yielded 0.87 g (54%) of **5** as light brown crystals, mp 228-231 °C; ir: 3427, 3156, 1688 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.50 (s, 3H, 1-CH_3), 3.63 (s, 3H, OCH_3), 3.98 (d, J = 14.5 Hz, 1H, 4-H), 4.78 (d, J = 14.5 Hz, 1H, 4-H), 5.10 (s, 1H, CH), 7.41-7.84 (m, 4H, phenyl protons), 8.10 (s, 1H, 2-H), 10.18 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2S$: C, 55.81; H, 4.68; N, 8.68. Found: C, 55.62; H, 4.74; N, 8.81.

10-(Methoxycarbonyl)-9*H*-pyrrolo[2,1-*d*][thiazolo[3,2-*a*][1,5]-benzodiazepin-5-ium Bromide (**6**).

This compound was obtained according to the general procedure for **2g,h** from compound **4** (1.2 g, 5.0 mmoles), the α-bromoacetaldehyde diethyl acetal (7.8 ml, 50 mmoles) and water (0.5 ml) in dry butan-2-one (100 ml). The mixture was refluxed for 3 hours. Recrystallization from anhydrous methanol/diethyl ether mixture yielded 0.9 g (48%) of **6** as deep brown crystals, mp >232 °C dec; ir: 1691 cm^{-1}; ^1H nmr (deuteriomethanol): δ 3.90 (s, 3H, OCH_3), 4.28 (d, J = 15.9 Hz, 1H, 9-H), 5.95 (d, J = 15.9 Hz, 1H, 9-H), 6.83 (d, J = 3.3 Hz, 1H, 11-H), 7.34 (d, J = 3.3 Hz, 1H, 12-H), 7.65-7.96 (m, 3H, 1-, 2-H and 3-H), 8.06 (m, 1H, 4-H), 8.28 (d, J = 4.0 Hz, 1H, 7-H), 8.75 (d, J = 4.0 Hz, 1H, 6-H); ^{13}C nmr (deuteriomethanol): δ 26.15 (CH_2), 52.06 (CH_3), 114.08 (CH), 115.28 (C), 123.31 (CH), 124.80 (CH), 126.87 (CH), 127.47 (CH), 130.10 (CH), 130.39 (C), 133.56 (C), 134.05 (CH), 134.23 (C), 139.14 (CH), 166.17 (CO), 171.54 (8a-C) ppm.

Anal. Calcd. for $C_{16}H_{13}BrN_2O_2S$: C, 50.94; H, 3.47; N, 7.43. Found: C, 60.07; H, 3.39; N, 7.31.

2-Methyl-4-thioxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbothialdehyde (**8**).

A suspension of 2.02 g (5.0 mmoles) of Lawesson's reagent in 100 ml of dry toluene was refluxed under stirring until the solution became clear. After this 1.9 g (10 mmoles) of lactam **7** [9] was added and the reaction mixture was refluxed for 4 hours, concentrated to half of its volume *in vacuo*, and was left in a refrigerator. Formed precipitate was collected and purified by recrystallization from benzene to give 1.2 g (55%) of **8**, mp 221-223 °C; ir: 3148 cm^{-1}; ^1H nmr (deuteriochloroform), two rotamers in a 10:1 ratio: δ 1.34 (d, J = 6.3 Hz, 3H, 2-CH_3), [1.40 (d, J = 6.5 Hz, 3H, 2-CH_3)], 2.93 (dd, J = 12.8, 12.9 Hz, 1H, 3-H), 3.21 (ddd, J = 0.8, 4.5, 13.1 Hz, 1H, 3-H), [4.83 (m, 1H, 2-H)], 5.85 (m, 1H, 2-H), 7.17-7.52 (m, 4H, phenyl protons), 9.32 (s, 1H, 1-CH), [9.65 (s, 1H, 1-CH)], 9.96 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 17.17 (CH_3), 48.62 (3-C), 59.86 (2-C), 122.44 (CH), [122.52], [126.53], 127.65 (CH), 128.19 (CH), 129.97 (CH), 134.89 (C), 135.86 (C), [190.25 (1-C)], 190.32 (1-C), 202.80 (4-C), [202.93 (4-C)] ppm.

Anal. Calcd. for $C_{11}H_{12}N_2S_2$: C, 55.90; H, 5.12; N, 11.85. Found: C, 56.20; H, 5.00; N, 11.67.

5-Acetyl-7-methyl-6,7,9,10,11,12-hexahydro-5*H*-[1,3]benzothiazolo[3,2-*a*][1,5]benzodiazepin-13-ium Chloride (**9**).

To a stirred solution of 0.5 g (2.0 mmoles) of **1d** in 40 ml of dry dioxane 1.32 g (10 mmoles) of α-chlorocyclohexanone was added and the solution was refluxed for 15 hours and allowed to stay at room temperature. The resulting precipitate was filtered and recrystallized from anhydrous methanol/diethyl ether mixture to give 0.60 g (76%) of **9**, mp 236-238 °C; ir: 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.63 (d, J = 6.0 Hz, 3H, 7-CH_3), 1.80 (s, 3H, CH_3CO), 2.00-3.46 (m, 8H, $(CH_2)_4$), 3.61-3.75 (m, 2H, CH, 7-H, 6-H), 4.68 (dd, J = 11.9, 11.5 Hz, 1H, 6-H), 7.50 (dd, J = 1.5, 7.6 Hz, 1H, 4-H), 7.71-7.82 (m, 2H, 2-H, 3-H), 8.36 (br d, 1H, 1-H); ^{13}C nmr (deuteriochloroform): δ 14.68 (7-CH_3), 21.13 (CH_2), 21.44 (CH_2), 22.55 (5-CH_3), 23.77 (CH_2), 24.79 (CH_2), 34.45 (7-C), 57.53 (6-C), 128.34 (CH), 129.70 (CH), 130.84 (CH), 131.88 (C), 132.63 (CH), 133.17 (C), 135.10 (C), 143.10 (C), 169.56 (CO), 175.48 (7a-C) ppm.

Anal. Calcd. for $C_{18}H_{21}ClN_2OS$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.75; H, 6.21; N, 8.12.

The Reaction of Compound **8** with α-Bromoacetaldehyde diethyl acetal.

To a stirred solution of 1.18 g (5.0 mmoles) of **8** in 50 ml of butan-2-one 4 ml (25.7 mmoles) of α-bromoacetaldehyde diethyl acetal and 0.5 ml of water were added. The mixture was refluxed for 10 minutes. After cooling to ambient temperature obtained precipitate was separated by filtration, washed with dry diethyl ether to give 0.7 g of a solid which, according to ^1H nmr spectrum, consisted of **12** and **2h** in a 1:1 ratio. Recrystallization from methanol afforded 0.2 g of **2h**, mp 247-249 °C. Mixed sample with authentic compound did not show depression of the melting point.

5-Methyl-6-thioformyl-4*H*,5*H*,6*H*-thiazolo[3,2-*a*][1,5]benzodiazepin-11-ium bromide (**12**).

^1H nmr (deuteriochloroform/deuteriomethanol, 4:1), two rotamers in a 4:1 ratio: δ 1.44 (d, J = 6.3 Hz, 3H, 5-CH_3), [1.51 (d, J = 6.3 Hz, 3H, 5-CH_3)], 3.18 (dd, J = 12.6, 15.3 Hz, 1H, 4-H), 4.12 (dd, J = 5.4, 15.3 Hz, 1H, 4-H), 5.93 (m, 1H, 5-H), 7.52-7.98 (m, 4H, phenyl protons), 8.32 (d, J = 4.0 Hz, 1H, 2-H), 8.60 (d, J = 4.0 Hz, 1H, 1-H), 9.31 (s, 1H, 6-CH), [9.53 (s, 1H, 6-CH)] ppm.

REFERENCES

[1] E. C. Cortes, M. J. B. Lopez and Y. M. O. Pichardo, *J. Heterocyclic Chem.*, **34**, 1833 (1997).

[2] A. Chimirri, R. Gitto, S. Grasso, A.-M. Monforte, G. Romeo and M. Zappala, *Heterocycles*, **36**, 601 (1993).

[3] L. H. Sternbach, *J. Med. Chem.*, **22**, 1 (1979).

[4] M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M. E. Marongiu, *Eur. J. Med. Chem.*, **36**, 935 (2001).

[5] M. Weber, W. Jäger and T. Erker, *J. Heterocyclic Chem.*, **40**, 851 (2003).

[6] R. Janciene, A. Vektariene, Z. Stumbreviciute, L. Kosychova, A. Klimavicius and B. D. Puodziunaite, *Heteroatom Chemistry*, **15**, 363 (2004).

[7] B. Puodziunaite, L. Kosychova, R. Janciene and Z. Stumbreviciute, *Monatsh. Chem.*, **128**, 1275 (1997).

[8] E. Müller, R. Haller and K. W. Merz, *Liebigs Ann. Chem.*, **697**, 193 (1966).

[9] B. A. Puodziunaite, R. A. Janciene and Z. A. Stumbreviciute, *Khim. Geterotsikl. Soedin.*, No. 7, 957 (1988); *Chem. Abstr.*, **110**, 135211e (1989).

[10] M. Zappala, A. Chimirri, S. Grasso, G. Romeo and A.-M. Monforte, *Farmaco*, **44**, 185 (1989).

[11] M. R. Grever, S. A. Schepart and B. A. Chabner, *Semin. Oncol.*, **19**, 622 (1992).