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2,3-Dihydro-1*H*-1,5-benzodiazepines: A Conversion of Thiolactams to Amidines

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Summary. The synthesis of a new series of diversely N-4 substituted amidines of 2,3-dihydro-1*H*-1,5-benzodiazepine has been accomplished starting from tetrahydro-1,5-benzodiazepin-2-one derivatives. These compounds were transformed into the desired thiolactams **2a–i** which reacted in the presence of mercuric chloride with ammonia, as well as primary or secondary amines to give amidines **3a–i**. Hydrazidines **3j–l** were prepared by treatment of thiolactams with an excess of hydrazine.

Keywords. 2,3-Dihydro-1*H*-1,5-benzodiazepines; Thiolactam; Amidine.

2,3-Dihydro-1*H*-1,5-benzodiazepine: Umwandlung von Thiolactamen in Amidine

Zusammenfassung. Einige neue N-substituierte Amidine von 2,3-Dihydro-1*H*-1,5-benzodiazepinen wurden ausgehend von Tetrahydro-1*H*-1,5-benzodiazepin-2-onen synthetisiert. Letztere wurden in die Thiolactame **2a–i** umgewandelt und anschließend durch Behandeln mit Ammoniak, primären oder sekundären Aminen in Gegenwart von Quecksilber(II)-chlorid zu den entsprechenden Amidinen **3a–i** umgesetzt. Die Hydrazinoamidine **3j–l** wurden aus den Thiolactamen mit Hydrazineüberschuß erhalten.

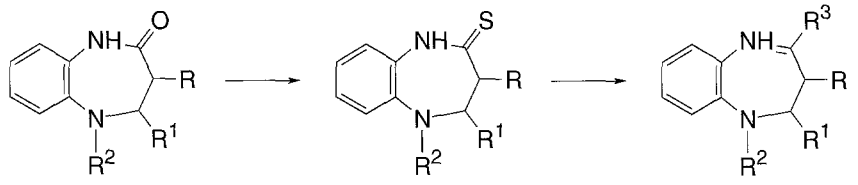
Introduction

The growing interest in the biological activities of condensed benzodiazepine systems [1, 2] prompted us to study the chemistry of tetrahydro-1,5-benzodiazepin-2-ones. Especially the examination of methods effecting transformations of the carbonyl group caught our attention. We have recently demonstrated that the N-1-C-2 lactam moiety of these compounds shows low reactivity towards primary or secondary amines [3]. As a further part of our chemical interest in this field, we turned towards the synthesis of the corresponding thiolactams and the nucleophilic replacement of the thione group.

Results and Discussion

The 1,5-benzodiazepine amidines **3** were synthesized using the route outlined in the Scheme. Thionation of lactams **1** to the desired thiolactams **2** was achieved by treatment with phosphorus pentasulfide in refluxing anhydrous pyridine. In this

way, compounds **2** were obtained routinely in a 60% overall yield. A similar reaction of **1c** and **1i** with *Lawesson*'s reagent in refluxing toluene yielded thiolactams **2c, i** in a lower yield, and about 50% of the starting lactams remained unchanged.



1a–i **2a–i** **3a–l**

1,2	R	R^1	R^2
a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me
e	Me	H	Me
f	H	Me	Me
g	H	H	CH_2Ph
h	Me	H	CH_2Ph
i	H	Me	CH_2Ph

3	R	R^1	R^2	R^3
a	H	Me	H	NH_2
b	Me	H	CH_2Ph	NH_2
c	H	Me	CH_2Ph	NH_2
d	H	H	CH_2Ph	NH-Pr-*n*
e	H	H	H	NH–C$_6$H$_{11}$
f	H	Me	CH_2Ph	NH–C$_6$H$_{11}$
g	H	H	Me	morpholino
h	H	Me	Me	morpholino
i	H	Me	H	piperidino
j	Me	H	H	$NHNH_2$
k	H	Me	H	$NHNH_2$
l	Me	H	Me	$NHNH_2$

Scheme

The thionamides served as common intermediates for further transformations towards the target amidine structures.

This type of reaction has been used for the preparation of amino compounds from the corresponding thionamides in the 1,4-benzodiazepine [4, 5], thieno[3, 4-*b*][1, 5]benzodiazepine [6], and pyrrolo-[2, 1-*c*][1, 4]benzodiazepine [7] series. It is apparent from a comparison of observations reported in the literature that the nature of the substituent or functional group and its position in the molecule relative to the thionamide group exert a considerable influence on the reactivity of the thione group. Thus, various thiolactams possess a different reactivity towards nucleophiles.

In the present work, the reaction of thiolactams **2** with ammonia, primary aliphatic or secondary heterocyclic amines, and hydrazine was investigated. Treatment of **2c,h,i** with ammonia in the presence of mercuric chloride in anhydrous *THF* gave the new amidines **3a–c**. Mercuric salts are known to favour this kind of reactions

[5,7]. The presence of mercuric chloride is required to enhance the reactivity of thiolactams **2a,d,f,g,i** with primary aliphatic amines such as propyl or cyclohexyl amines and also with secondary amines such as morpholine or piperidine to give the desired N-substituted amidines **3d–h**, respectively. An alternative method the preparation of amidines **3g** and **3i** relies on the reaction of thiolactams **2d,c** with the appropriate secondary amine in a refluxing mixture of ethanol and dimethyl sulfoxide for 12 h. Products **3g,i** were also obtained in low yields. During the course of our work it was found that under mild conditions compounds **2b,c,e** can be transformed into the new hydrazidines **3j–l** by condensation with hydrazine in ethanol at room temperature.

The precursors **1a–c** [8] and **1d–f** [9] were previously described by us, and lactams **1d–f** have been prepared now according to the previously reported method [10]; however, reaction temperature and purification procedures were modified. Compounds **1d–f** were separated from the 1,5-dimethyl derivatives by recrystallization in a 40–55% overall yield. The synthesis of **1i** is described in Ref. [3], and **1g,h** were obtained in the same way by alkylation of **1a,c** with benzyl chloride in the presence of sodium hydrocarbonate.

It should be noted that in the ^{1}H NMR spectra of thiolactams **2a–i** the diazepine protons nearest to the C = S moiety more deshielded than analogous protons in the spectra of the corresponding lactams **1a–i** [8, 9, 10]. The chemical shift values show that the 1-NH proton signals ($\Delta\delta = 1.4$–2.2 ppm) and the 3-CH_2 proton signals ($\Delta\delta = 0.5$–7 ppm) are moved downfield. In the spectra of compounds **2e,f,i**, a long-range proton-proton spin-spin coupling over four bonds (H-N-C(S)-C-H; $^4J = 1.0$ Hz) was observed. This behaviour is attributed to a slower interconversion between the two conformations of the benzodiazepine ring compared to compounds **2a,d,g**.

The structures of all compounds were confirmed by elemental analyses and spectroscopic measurements (IR, ^{1}H NMR). All elemental analyses (C, H, N) are in accordance ($\pm 0.35\%$) with the calculated values.

Experimental

Melting points were determined in open capillary tubes with a PTP apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a 71 IR spectrophotometer. ^{1}H NMR spectra were measured on a Hitachi R-22 spectrometer operating at 90 MHz (35°C) with *HMDSO* as an internal reference; chemical shifts are expressed in ppm. TLC was performed on *Silufol* UV_{254} silica gel plates in the system chloroform – ethyl acetate – methanol (14:7:1).

*3-R-4-R^1-5-R^2-2,3,4,5-Tetrahydro-1H-1,5-benzodiazepin-2-thiones (**2a–i**); General procedure*

Phosphorus pentasulfide (25.0 mmol) in 100 ml of anhydrous pyridine was stirred and heated at 80°C for 2 h with protection from atmospheric moisture. To the warm clear solution, the appropriate lactam **1a–i** (25 mmol) was added, and the mixture was heated at 80°C for 2 h or for 4 h (compounds **2g–i**) under stirring (TLC). The obtained turbid reaction mixture was concentrated to dryness *in vacuo*. The resulting tarry residue was rapidly chilled in an ice-cold water bath, and 200 g of crushed ice was added. The residue was intensively ground until the formation of precipitate was observed. Then, three 100 ml portions of cold water and 200 g of ice were added over 1 h under good stirring. The precipitate was separated by filtration, washed with cold water, and dried. The well dried crude product was recrystallized from an appropriate solvent. Tiolactams **2a–i** were obtained as pale yellow crystals.

Table 1. Experimental data for compounds **1–3**

	Yield (%)	M.p. (°C) (solvent)	Molecular formula (MW)	IR (cm^{-1})
1g	67	137–138 (Benzene)	$C_{16}H_{16}N_2O$ (252.31)	
1h	77	128–130 (Benzene)	$C_{17}H_{18}N_2O$ (266.35)	
2a	60	161–162 (*o*-Xylene)	$C_9H_{10}N_2S$ (178.26)	1605, 1585, 1550, 1510, 3330, 3175, 3110, 3030
2b	62	198–200 (MeOH)	$C_{10}H_{12}N_2S$ (192.27)	1585, 1540, 1495, 3310, 3155, 3110
2c[a]	66	129–130 (MeOH)	$C_{10}H_{12}N_2S$ (192.27)	1590, 1545, 1535, 1495, 3340, 3130, 3090
2d	64	153–155 (MeOH)	$C_{10}H_{12}N_2S$ (192.28)	1598, 1580, 1540, 1495, 3150, 3090
2e	72	137–139 (MeOH)	$C_{11}H_{14}N_2S$ (206.31)	1597, 1575, 1535, 1495, 3135, 3080
2f[a]	70	154–156 (*o*-Xylene)	$C_{11}H_{14}N_2S$ (206.31)	1595, 1580, 1540, 1490, 3145, 3085
2g	67	123–125 (Benzene)	$C_{16}H_{16}N_2S$ (268.38)	1605, 1580, 1555, 1515, 3135, 3095
2h	62	164–165 (Benzene)	$C_{17}H_{18}N_2S$ (282.40)	1595, 1535, 1490, 3115 3070
2i	70	144–146 (Benzene)	$C_{17}H_{18}N_2S$ (282.40)	1595, 1535, 1490, 3145 3080
3a	54	154–156 (AcOEt:Et_2O = 1:5)	$C_{10}H_{13}N_3$ (175.24)	
3b	55	54–56 (dec) (Et_2O:Hexane = 1 : 5)	$C_{17}H_{19}N_3$ (265.36)	
3c	58	50–52 (dec) (Et_2O:Hexane = 1:5)	$C_{17}H_{19}N_3$ (265.36)	
3d	48	113–115 (MeOH:H_2O = 1 : 10)	$C_{19}H_{23}N_3$ (293.42)	
3e	50	125–127 (Et_2O)	$C_{15}H_{21}N_3$ (243.35)	
3f	52	160–162 (Et_2O)	$C_{23}H_{29}N_3$ (347.51)	
3g	35	42–44 (Et_2O:Hexane = 10 : 1)	$C_{14}H_{19}N_3O$ (245.32)	
3h	48	76–78 (Et_2O)	$C_{15}H_{21}N_3O$ (259.55)	
3i	30	63–64 (Et_2O)	$C_{15}H_{21}N_3$ (243.35)	
3j	50	54–56 (Abs. Et_2O)	$C_{10}H_{14}N_4$ (190.25)	
3k	75	146–148 (Abs. Et_2O)	$C_{10}H_{14}N_4$ (190.25)	
3l	50	106–110 (Abs. Et_2O)	$C_{11}H_{16}N_4$ (204.28)	

[a] Ref. [11]: only ^1H NMR data

Reaction of lactams **1c,i** *with Lawesson's reagent*

A suspension of *Lawesson*'s reagent (10 mmol) in 150 ml of dry toluene was refluxed under stirring until the solution became clear. It was then allowed to cool to 40°C, and a warm solution of **1c,i** (20 mmol) in 70 ml of dry toluene was added. The reaction mixture was refluxed for 6 h, concentrated to half of its volume *in vacuo*, and allowed to cool to ambient temperature. The formed precipitate was collected and refluxed in 50 ml of xylene. The hot solution was filtered from the insoluble phosphorus by-product. After cooling, the precipitate was filtered and dried. The ^{1}H NMR spectrum indicated the mixture of equal amounts of thiolactam (**2c,i**) and starting compound (**1c,i**).

*1-R^2-2-R^1-3-R-2,3-Dihydro-1H-1,5-benzodiazepine-4-amines (***3a–h***); General procedure*

A solution of thiolactam **2a,c,d,e,g–i** (10 mmol) in 100 ml of dry *THF* was warmed to 55°C. A stream of ammonia was bubbled through this solution (compounds **3a-c**), or an appropriate amine (200 mmol) was added (compounds **3d–i**). Mercuric chloride (4.0 g, 15 mmol) was incorporated in one portion, the reaction mixture turning black immediately. In the case of compounds **3a–c**, the stream of ammonia was stopped after 10 min. The reaction mixture was stirred at room temperature

Table 2. ^{1}H NMR data for compounds **1** and **2** ($CDCl_3$)

	δ (ppm), J (Hz)
1g	2.45 (bt, 2H, CH_2CO), 3.36 (bt, 2H, CH_2N), 4.21 (s, 2H, CH_2Ar), 6.76–7.34 (m, 9H, Ar), 9.28 (bs, 1H, NH)
1h	0.98 (d, 3H, CH_3), 2.75 (m, 1H, CH), 3.16 (dd, $^2J = 11.8, ^3J = 6.0$, 1H, CH_2CH), 3.32 (dd, $^3J = 12.0$, 1H, CH_2CH), 4.08 and 4.45 (AB-q, 2H, CH_2Ar), 6.84–7.42 (m, 9H, Ar), 8.36 (bs, 1H, NH)
2a	3.07 (m, 2H, CH_2CS), 3.69 (bs, 1H, $NHCH_2$), 3.75 (m, 2H, CH_2N), 6.56–7.26 (m, 4H, Ar), 9.85 (bs, 1H, NHCS)
2b	1.23 (d, 3H, CH_3), 3.00 (bs, 1H, NHCH), 3.04 (m, 1H, CH), 3.39 (dd, $^2J = 12.0, ^3J = 8.0$, 1H, CH_2), 3.59 (dd, $^3J = 4.0$, 1H, CH_2), 6.57–7.13 (m, 4H, Ar), 9.47 (bs, 1H, NHCS)
2c	1.33 (d, 3H, CH_3), 2.81 (dd, $^2J = 13.4, ^3J = 7.8$, 1H, CH_2), 3.12 (ddd, $^3J = 4.0, ^4J = 1.0$, 1H, CH_2), 3.42 (bs, 1H, NHCH), 4.06 (m, 1H, CH), 6.68–7.19 (m, 4H, Ar), 10.17 (bs, 1H, NHCS)
2d	2.76 (s, 3H, CH_3), 2.90 (bt, 2H, CH_2CS), 3.60 (bt, 2H, CH_2N), 6.79–7.32 (m, 4H, Ar), 10.48 (bs, 1H, NH),
2e	1.24 (d, 3H, CH_3C), 2.75 (s, 3H, CH_3N), 2.88 (m, 1H, CH), 3.25 (dd, $^2J = 10.0, ^3J = 5.0$, 1H, CH_2), 3.44 (dd, $^3J = 12.0$, 1H, CH_2), 6.84–7.23 (m, 4H, Ar), 10.32 (s, 1H, NH)
2f	1.04 (d, 3H, CH_3CH), 2.62 (dd, $^2J = 12.0, ^3J = 9.0$, 1H, CH_2CS), 2.78 (s, 3H, CH_3N), 2.97 (ddd, $^3J = 5.3, ^4J = 1.0$, 1H, CH_2), 3.97 (m, 1H, CH), 6.74–7.33 (m, 4H, Ar), 10.39 (bs, 1H, NH)
2g	2.89 (bt, 2H, CH_2CS), 3.47 (bt, 2H, CH_2N), 4.14 (s, 2H, CH_2Ar), 6.78–7.33 (m, 9H, Ar); 10.72 (bs, 1H, NH)
2h	1.14 (d, 3H, CH_3), 2.76–3.45 (m, 3H, CH_2CH), 4.01 and 4.48 (AB-q, 2H, CH_2Ar), 6.82–7.28 (m, 9H, Ar), 10.39 (bs, 1H, NH)
2i	1.02 (d, 3H, CH_3), 2.61 (dd, $^2J = 12.2, ^3J = 11.2$, 1H, CH_2CS), 2.95 (ddd, $^3J = 5.3, ^4J = 1.0$, 1H, CH_2CS), 4.05 (m, 1H, CH), 4.26 (s, 2H, CH_2Ar), 6.75–7.35 (m, 9H, Ar), 10.17 (bs, 1H, NH)

until TLC analysis indicated the completion of the reaction (1.5–7 h). Mercuric sulfide was filtered off, the filtrate was evaporated to dryness *in vacuo*, and the residue was dissolved in ethyl acetate. The organic solution was washed with a saturated aqueous solution of sodium thiosulfate, dried (Na_2SO_4), and concentrated to give the corresponding crude amidine. Crystallization from an appropriate solvent afforded pure crystalline compounds **3** except **3b,c** which were obtained as colorless foamy solids and **3i** (greyish solid). Compound **3b** is stable for one and a half months.

*1-Methyl-4-morpholino- and 2-Methyl-4-piperidino-2,3-dihydro-1H-1,5-benzodiazepines (**3g** and **3i**)*

A solution of thiolactam **2d,c** (10 mmol) and morpholine or piperidine (20 mmol) in a mixture of 30 ml of methanol and 6 ml of dimethyl sulfoxide was refluxed until the evolution of hydrogen

Table 3. ^{1}H NMR data for compounds **3** (**3a–c** in acetone-d_6, **3d–l** in $CDCl_3$)

	δ (ppm), J (Hz)
3a	1.20 (d, 3H, CH_3), 2.10 (dd, $^2J = 13.4, ^3J = 7.2$, 1H, CH_2), 2.41 (dd, $^3J = 5.0$, 1H, CH_2), 4.01 (m, 1H, CH), 3.65–4.35 (bs, 3H, NH, NH_2), 6.54–6.89 (m, 4H, Ar)
3b	1.02 (d, 3H, CH_3), 2.56–2.78 (m, 1H, C*H*CH_2), 3.04–3.38 (m, 2H, C*H*$_2$CH), 3.48 (bs, 2H, NH_2), 4.00 and 4.34 (AB-q, $^2J = 14.2$, 2H, CH_2Ar), 6.71–7.40 (m, 9H, Ar)
3c	1.01 (d, 3H, CH_3), 1.89–2.40 (m, 2H, C*H*$_2$CH), 3.37 (bs, 2H, NH_2), 3.86 (m, 1H, CH), 4.29 (s, 2H, CH_2Ar), 6.69–7.40 (m, 9H, Ar)
3d	0.93 (t, 3H, CH_3), 1.64 (m, 2H, C*H*$_2$CH$_3$), 2.22 (t, 2H, CH_2C=), 3.29 (t, 2H, CH_2N), 3.40 (t, 2H, CH_2N), 3.24–3.45 (bs, 1H, NH), 4.16 (s, 2H, CH_2Ar), 6.79–7.41 (m, 9H, Ar)
3e	0.82–2.29 (m, 10H, 5CH_2-cycl), 2.27 (t, 2H, CH_2C=), 3.26 (bs, 1H, NH), 3.64 (t, 2H, CH_2N), 3.85 (m, 1H, CH), 4.38 (bs, 1H, NH), 6.51–7.03 (m, 4H, Ar)
3f	0.97 (d, 3H, CH_3), 1.00–2.39 (m, 12H, 5CH_2-cycl, C*H*$_2$CH), 3.76 (m, 1H, C*H*CH_3), 3.85–4.40 (m, 2H, CH-cycl, NH), 4.25 (s, 2H, CH_2Ar), 6.81–7.44 (m, 9H, Ar)
3g	2.34 (bt, 2H, CH_2C=), 2.65 (s, 3H, CH_3), 3.29 (bt, 2H, CH_2N), 3.31–3.68 (m, 8H, 4CH_2-morph), 6.77–6.91 (m, 4H, Ar)
3h	1.08 (d, 3H, C*H*$_3$CH), 2.16 (dd, $^2J = 13.7, ^3J = 9.6$, 1H, CH_2C=), 2.44 (dd, $^3J = 5.3$, 1H, CH_2C=), 2.74 (s, 3H, CH_3N), 3.46–3.96 (m, 9H, 4CH_2-morph, CH), 6.80–7.01 (m, 4H, Ar)
3i	1.14 (d, 3H, C*H*$_3$CH), 1.57 (m, 6H, 3CH_2-piper), 2.20 (dd, $^2J = 13.7$, $^3J = 7.6$, 1H, CH_2C=), 2.44 (dd, $^3J = 5.2$, 1H, CH_2C=), 3.19 (bs, 1H, NH), 3.51 (m, 4H, CH_2NCH_2), 3.89 (m, 1H, CH), 6.56–7.03 (m, 4H, Ar)
3j	1.05 (d, 3H, CH_3), 2.30–3.25 (m, 3H, CH_2CH), 3.40–4.90 (bs, 4H, NH_2, 2NH), 6.30–7.20 (m, 4H, Ar),
3k	1.23 (d, 3H, CH_3), 2.22 (dd, $^2J = 13.9, ^3J = 7.2$, 1H, CH_2), 2.52 (dd, $^3J = 5.2$, 1H, CH_2), 3.83 (m, 1H, CH), 2.95–4.70 (bs, 4H, NH_2, 2NH), 6.61–7.00 (m, 4H, Ar)
3l	1.14 (d, 3H, CH_3), 2.35–3.45 (m, 3H, CH_2CH), 2.77 (s, 3H, CH_3), 3.00–4.10 (bs, 3H, $NHNH_2$), 6.75–7.20 (m, 4H, Ar)

sulfide ceased (12 h). The solvent was concentrated to dryness *in vacuo*, and the residue was dissolved in ether. The organic layer was extracted with dilute hydrochloric acid, the aqueous layer was made basic with sodium hydroxide, extracted with ether, and dried. The ether solution was concentrated to give the residue which was recrystallized from an appropriate solvent and formed **3g** and **3i** as solids (20% and 27% yields, respectively). M.p.s were identical with those of authentic samples. Compound **3g** was also characterized as its hydrochloride; m.p.: 120–121°C (dec).

*1-R^2-2-R^1-3-R-4-Hydrazino-2,3-dihydro-1H-1,5-benzodiazepines (**3j–l**); General procedure*

A solution of thiolactam **2b,c,e** (3.76 mmol) in 30 ml of methanol and 2 ml of hydrazine hydrate (80%) was stirred at room temperature until TLC analysis indicated completion of the reaction. The solvent was evaporated to dryness *in vacuo*, and the residue was dissolved in ether. The organic solution was dried (Na_2SO_4) and concentrated to give the crude amidine. Crystallization from an appropriate solvent afforded compounds **3j–l** as gray crystals which became darker on storage.

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