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Functionalization of 2,3,4,5-Tetrahydro-1,5-benzodiazepin-2(1*H*)-ones by Electrophilic Aromatic Substitution

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Summary. Highly substituted, novel, 8- and 9-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-ones were obtained by direct nitration of the 7-bromo-5-trifluoroacetyl (or formyl)-substituted tetrahydrobenzodiazepinones. Alkaline and acidic hydrolysis of the novel mononitro derivatives was examined. Semiempirical AM1 calculations of aromatic substituents orientation in the nitration products are presented.

Keywords. 2,3,4,5-Tetrahydro-1,5-benzodiazepin-2(1*H*)-ones; Electrophilic substitution; Hydrolysis; Semiempirical calculations.

Introduction

Polycyclic compounds containing the 1,5-benzodiazepine system are known to elicit a wide range of biological activities [1, 2]. Recently, we have disclosed the properties of some imidazo[1,5,4-*e,f*][1,5]benzodiazepines as inhibitors of HIV-1 replication [3]. These derivatives are nearest analogs of well-known imidazo[1,4]-benzodiazepines readily identifiable by the acronym TIBO [4]. Several analogs of the parent TIBO, halogenated in the aromatic ring, have been studied and demonstrated anti-HIV activity at low concentrations [5, 6].

In connection with a synthesis project directed toward the preparation of *peri*-annelated 1,5-benzodiazepines bearing the imidazole nucleus condensed both to the seven-membered heterocycle and the aromatic ring, we desired an efficient route to novel 9-nitro substituted dihydro- or tetrahydro-1,5-benzodiazepinones. One of the approaches to such compounds can be achieved from a precursor having the necessary substituent incorporated *prior* to the synthesis of the desired heterocycle. More

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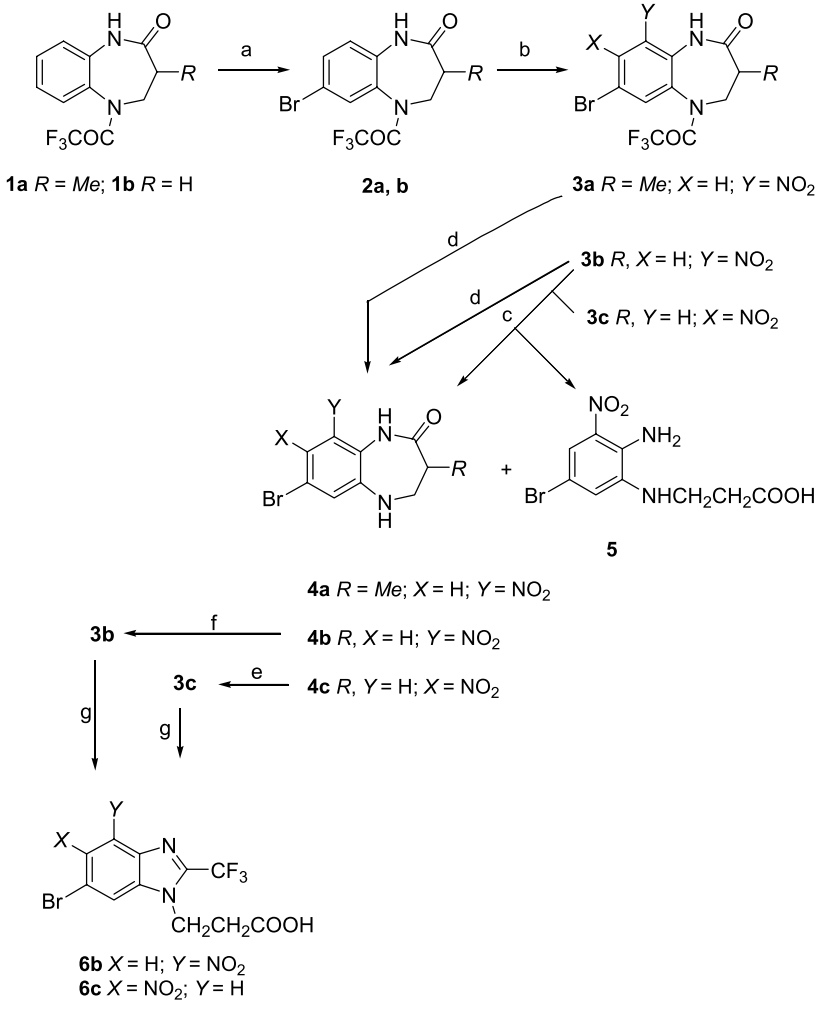
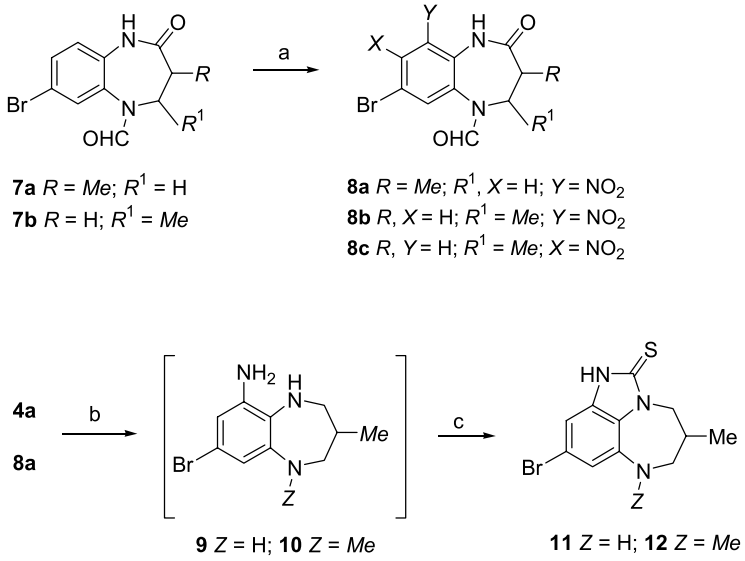
recently the reaction of 3-nitro-1,2-phenylenediamine with ethyl acetoacetate has been examined by us [7]. It has been stated that condensation reaction leads to the mixture of dihydro-4-methyl-9-(and 6)-nitro-1,5-benzodiazepinones and a variety of additional products. The present study details our efforts to functionalize the tetrahydrobenzodiazepinone skeleton by direct nitration, including variation of substituents in the diazepine ring (N-5, C-3, and C-4). An MO LCAO calculation study was employed to estimate the regioselectivity of electrophilic aromatic substitution.

Results and Discussion

It has previously been reported that nitration or bromination of 5-acyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-ones leads to 7-substituted derivatives [8, 9] and that 5-acetyl-7-bromo-substituted 1,5-benzodiazepinones are nitrated in



Scheme 1. Reagents and conditions: (a) Br_2, *Ac*OH, H_2SO_4, rt; (b) KNO_3/H_2SO_4, $-18°C \rightarrow$ rt; (c) 1*N* NaOH, *Et*OH, rt; (d) NH_4OH, *Et*OH, rt; (e) considerable excess of $(CF_3CO)_2O$, $ClCH_2CH_2Cl$-*THF*, 90°C; (f) 1.3 equiv of $(CF_3CO)_2O$, CH_2Cl_2, rt; (g) conc. HCl, *Ac*OH, rt



7a *R* = *Me*; R^1 = H
7b *R* = H; R^1 = *Me*

8a *R* = *Me*; R^1, *X* = H; *Y* = NO_2
8b *R*, *X* = H; R^1 = *Me*; *Y* = NO_2
8c *R*, *Y* = H; R^1 = *Me*; *X* = NO_2

9 *Z* = H; **10** *Z* = *Me*

11 *Z* = H; **12** *Z* = *Me*

Scheme 2. Reagents and conditions: (a) KNO_3/H_2SO_4, $-18°C \rightarrow$ rt; (b) $LiAlH_4$, *THF*, reflux; (c) CS_2, *THF*, rt

position 9 [3]. It has been also noted that nitration of 7-chloro-5-(3-nitrophenyl)-1,3,4,5-tetrahydro-1,4-benzodiazepin-2(2*H*)-one affords the corresponding 9-nitro tetrahydro derivative [10]. Our initial goal was the preparation of compounds of type **3** and **8** (Schemes 1 and 2) containing trifluoroacetyl or formyl, as the appropriate blocking groups, at N-5 position.

Benzodiazepinones **2a**, **2b** were readily prepared from the corresponding 2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-one and 3-methyl homologue [11] by acylation with trifluoroacetic acid anhydride in an organic solvent and subsequent bromination of the obtained **1a** and **1b** with bromine in a mixture of acetic acid and concentrated sulfuric acid following the previously reported procedures [11, 9]. The nitration of **2a** and **2b** using 2 molar equivalents of potassium nitrate in cold concentrated sulfuric acid gave rise to a mixture of the isomeric mononitro products **3**. Monitoring the progress of the reaction by TLC showed the formation of two products. An examination of the ^{1}H NMR spectra for the crude nitration products showed a mixture of 8- and 9-nitro isomers, present in a ratio of about 1:4 and 1:3. The position of the nitro group was determined from the splitting pattern and coupling constants for the aromatic protons. In the spectra chemical shifts of aromatic protons from the mixtures are between 7.73–8.41 ppm which appeared as two pairs of signals. The observed $J = 2.2$ Hz for the aromatic protons at C-6 and C-8 indicated that they are situated in *meta*-position in 9-nitro derivatives, whereas protons at C-9 and C-6 showed two singlets for protons at *para*-position in 8-nitro derivatives. It is worth noting that in the spectra of compounds **2a**, **3a**, **3b**, and **3c** the interaction of H-6 with the $COCF_3$ group was seen. Therefore H-6 proton signals are observed as unresolved multiplets.

The desired 9-nitro derivatives **3a** and **3b** were obtained by crystallization of the resultant crude mixtures in 51 and 36% yields. After separation of **3b** and

evaporation of the mother liquid the resulting solid residue was subjected to alkaline hydrolysis. Treatment with 1 *N* NaOH in ethanol at room temperature gave the N_5-unblocked product **4c** as the major product along with the unexpected product **5**, which could be formed from the negligible amount of the deprotected 9-nitro isomer **4b**. Thus, cleavage of the diazepinone ring was found to take place. In the ^{1}H NMR spectrum of **5** the presence of two doublets at 6.59 and 7.39 ppm ($J = 2.0$ Hz) confirmed its origin from the 9-nitro derivative **3b**. The appearance of two triplet signals of $-CH_2-CH_2-$ protons at 2.57 and 3.29 ppm (A_2X_2 system) being different from those of the benzodiazepine framework is in agreement with the suggested structure. Likewise, evidence of the structure **5** is given by the presence of a one-proton broad singlet at $\delta = 5.63$ and a two-proton one at 7.26 ppm, that could be exchanged with D_2O. This is consistent with the formation of a primary and secondary amine. Nevertheless, **4a** and **4b** could be obtained in 83 and 63% yields upon treatment of **3a** and **3b** with concentrated ammonia-water at room temperature.

The separation of N_5-unblocked isomeric nitro-substituted derivatives **4b** and **4c** confirmed also the presence of two components in the **2b** nitration mixture, but we were unable to isolate **3c** from the mixture. It prompted us to perform an opposing reaction. Preparation of **3b** and **3c** was accomplished by different procedures. Treatment of **4b** with 1.3 molar equivalents of trifluoroacetic acid anhydride in an organic solvent at room temperature afforded **3b**. The acylation of **4c** under these conditions and even on heating showed that no reaction occurred. More conveniently, **4c** was converted to **3c** when a considerable excess of the acylating agent was used. These results confirm the different nucleophility of the N-5 nitrogen atom in the 9- and 8-nitro isomers **4b** and **4c**. The position *para* to the nitro group of N-5 in **4c** is consistent with the electron-withdrawing effect of the nitro group decreasing the nucleophility of this nitrogen atom.

Upon treatment of **3b** and **3c** with hydrochloric acid in acetic acid the rearrangement of the benzodiazepinone skeleton occurred and compounds **6b** and **6c** could be isolated. Tetrahydro-1,5-benzodiazepinones are somewhat unstable in acidic medium involving the hydrolysis of the cyclic lactamic bond [12]. Thus, these results showed that an intermediate, which is almost certainly formed by splitting of the NH–CO– bond in compounds **3** cyclise with loss of water to a five-membered heterocycle. Such rearrangement to the analogous 2-methylbenzimidazole derivative was observed on bromination of 5-acetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-one in acidic medium [9]. It is worth noting that the nature of the alkyl substituent in the benzimidazole derivative is determined by the acyl group (in our case trifluoroacetyl group) present at the N-5 atom. In the ^{1}H NMR spectra of **6b** and **6c** the presence of protons of two methylene groups of a $-CH_2-CH_2-$ fragment, which resonate as two triplets at $\delta = 2.85$ and 4.69 ppm confirmed the presence of the propionic acid chain in these compounds.

Our early observation that nitration of *N*-acetyl-substituted tetrahydro-benzodiazepinones took place selectively at C-9 [3] led to the expectation that nitration of the analogous *N*-formyl-substituted derivatives could also be directed to C-9 if the C-7 position was blocked. Thus, 7-bromo-5-formylbenzodiazepinones **7a** and **7b**, which have been previously synthesized [11], were chosen as the substrates. Nitration of **7a** in an analogous fashion to **2** afforded a mixture of 8- and 9-mononitro products in a ratio of 1:4. After crystallization of the mixture the 9-nitro

isomer **8a** was obtained in 61% yield. Reaction of **7b** with the nitration agent led also to a mixture of 9- and 8-nitro compounds **8b** and **8c** in a ratio from 1 to 1.2, which was separated by fractional crystallization.

With **4a** and **8a** as key intermediates in hand we were able to complete the synthesis of the *peri*-annelated heterosystem. Thus, the fully reduced aminobenzodiazepines **9** and **10** were obtained from **4a** and **8a** by one-pot reduction of both nitro group and carbonyl groups with $LiAlH_4$. These intermediates were utilized without isolation in the cyclization for the synthesis of the tricyclic thiones **11** and **12** by treatment with carbon disulfide.

Since nitration of 7-brominated tetrahydro-1,5-benzodiazepinones **2a**, **2b** and **7a**, **7b** bearing trifluoroacetyl or formyl groups at N-5 and a methyl substituent at C-3 or C-4 of the diazepine ring did not occur regioselectively we investigated the situation by means of a semiempirical method extending our study by the previously described 5-acetyl-7-bromo-substituted tetrahydro-1,5-benzodiazepinones **13**–**15** [3]. For this purpose, we used several approaches to evaluate the reactivity of aromatic moiety of the molecules [13–15]. Geometry optimization of the derivatives was carried out with the semiempirical AM1 method [16]. The computational results (Table 1) indicate that for all derivatives the atomic charge densities on the aromatic carbon atoms decrease in the following way: C-7 > C-9 > C-8 > C-6. This suggests that position 9 (−0.177) is susceptible to electrophilic attack when position 7 is occupied. The total p_z electron population density is mostly located at C-9 (1.059) and less density is at C-8 (0.960). This approach indicated no more than a common tendency of the nitration reaction direction. Likewise, in experiments the nitration process of all studied compounds took place predominantly at C-9. However, this parameter does not propose any evidence that nitration could occur at position 8, whereas 8-nitro derivatives were also obtained in practice. The

Table 1. Calculated atomic charge densities, total p_z *e*lectron population densities, electron population densities of HOMO and differences ($\Delta\Lambda^+$, kJ/mol) of π-localization energies of transition state σ-complex at the C-8 and C-9 atoms of compounds **2a**, **2b**, **7a**, **7b**, and **13**–**15** (AM1 approximation)

Compd.	Atomic charge densities		p_z		HOMO		$\Delta\Lambda^+$/ kJ mol^{-1}
	C-8	C-9	C-8	C-9	C-8	C-9	
2a	−0.071	−0.177	0.9561	1.0604	0.0797	0.0498	8.5
2b	−0.067	−0.178	0.9498	1.0580	0.0593	0.0514	6.3
7a	−0.078	−0.177	0.9647	1.0625	0.0694	0.0424	13.3
7b	−0.075	−0.177	0.9592	1.0559	0.0613	0.0493	0.7
13*	−0.077	−0.177	0.9628	1.0601	0.0680	0.0434	23.5
14*	−0.078	−0.178	0.9610	1.0560	0.0685	0.0434	22.1
15*	−0.080	−0.176	0.9672	1.0602	0.0727	0.0357	19.8

* Compounds: 5-acetyl-7-bromo-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-one (**13**); 5-acetyl-7-bromo-4-methyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-one (**14**); 5-acetyl-7-bromo-3-methyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1*H*)-one (**15**)

electron population densities of the HOMO could be interpreted that for nitration reactions substitution at C-8 is also possible.

In the next step π-localization energies for transition state σ-complexes were calculated. The difference between π-localization energies ($\Delta\Lambda^+$, kJ/mol) at positions 9 and 8 are presented in Table 1. The $\Delta\Lambda^+$, being $19.8 \div 23.5$ kJ/mol for *N*-acetyl derivatives **13**–**15**, indicated that C-9 is more favorable for the formation of a σ-complex than C-8. The predictions of exceptional reactivity of C-9 atom towards NO_2^+ in **13**–**15** has been experimentally confirmed since substitution at C-8 was not detected. In the case of nitration of the *N*-formyl derivative **7b** π-localization energies differ only by $\Delta = 0.7$ kJ/mol and it correlates with the experiment showing that two mononitro compounds (**8b** and **8c**) were formed in almost equal ratio. The $\Delta\Lambda^+$ for **2a**, **2b**, and **7a** is in the range of $6.3 \div 13.3$ kJ/mol. The smaller $\Delta\Lambda^+$ values for **2a**, **2b**, and **7a** in comparison with those for **13**–**15** yielded satisfying correlation with experiments, which confirmed the formation of both possible nitro isomers, though the substitution at C-9 is favored (9-nitro isomers predominate in the crude nitration mixtures). Moreover, it is worth noting that the $\Delta\Lambda^+$ for **7a** and **7b** is 13.3 and 0.7 kJ/mol. The structures of those compounds differ only by the position of the methyl substituent at C-3 or C-4 atoms of the heterocycle, and presumably, this may explain the distinct contribution of this substituent to the stability of transition state σ-complex. Generally, there is a correlation between calculated π-localization energies of the transition state σ-complex and the nature of substituents. The calculations evidently point to the suitability of this parameter to predict the reactivity of differently substituted tetrahydro-1,5-benzodiazepinones in electrophilic aromatic substitution.

Experimental

^{1}H NMR spectra were taken on a Tesla BS 570 A (80 MHz) spectrometer using *TMS* as internal standard. IR spectra were obtained of KBr pellets on a Perkin-Elmer FT spectrophotometer Spectrum GX. TLC was performed on Silufol UV_{254} silica gel plates in the system $CHCl_3$:*Et*OAc:*Me*OH (14:7:1). Dry column vacuum chromatography was performed with silica gel Chemapol L 5/40 mesh. Melting points were determined in open capillary tubes and are uncorrected. Organic layers from aqueous extractions were dried over $MgSO_4$ and concentrated in vacuum. AM1 calculations were carried out by GAMESS version 1998 package [16]. Minima and transition states were characterized by vibrational frequency calculations. π-Localization energies were calculated for models of transition state σ-complex in accordance to Ref. [15]. The experimental values of microanalyses for the new compounds **1**–**8**, **11**, and **12** agreed with the calculated ones. Compounds **1b**, **2b**, and **7a**, **7b** were synthesized according to Refs. [9, 11].

3-Methyl-5-trifluoroacetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**1a**, $C_{12}H_{11}F_3N_2O_2$)

A solution of 3-methyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one [11] (3.6 g, 20 mmol) and 4.2 cm^3 of trifluoroacetic acid anhydride (6.3 g, 30 mmol) in 150 cm^3 of dry CH_2Cl_2 was stirred at room temperature for 2 h. The reaction mixture was washed with H_2O, dried, and evaporated to dryness. The solid residue was recrystallized.

Yield: 4.5 g (83%); mp 129–131°C (CCl_4); white crystals; IR: $\bar{\nu} = 3207$, 3152 (NH), 1708, 1673 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.17$ (d, $J = 6.8$ Hz, CH_3), 2.83 (m, CH), 3.70 (m, 1H, CH_2), 4.55 (m, 1H, CH_2), 7.05–7.60 (m, 4H, C_6H_5), 8.43 (bs, NH) ppm.

7-Bromo-3-methyl-5-trifluoroacetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**2a**, $C_{12}H_{10}BrF_3N_2O_2$)

The reaction of **1a** (5.4 g, 20 mmol), 2 cm^3 of Br_2 (3.2 g, 40 mmol) and 2 cm^3 of conc. H_2SO_4 in 30 cm^3 of *Ac*OH according to the Ref. [9] gave **2a**. Yield: 4.5 g (64%); mp 168–170°C (C_6H_6); white crystals; IR: $\bar{\nu} = 3179$ (NH), 1708, 1681 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.16$ (d, $J = 6.8$ Hz, CH_3), 2.81 (m, CH), 3.69 (m, 1H, CH_2), 4.53 (m, 1H, CH_2), 7.08 (d, $J = 8.8$ Hz, H-9), 7.46 (m, H-6), 7.58 (dd, $J = 2.2$, 8.8 Hz, H-8), 8.62 (bs, NH) ppm.

General Procedure for the Nitration of 7-Bromo-5-trifluoroacetyl(or formyl)-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-ones **2a**, **b** *and* **7a**, **b**

A solution of 10 mmol of compound **2a**, **2b**, **7a**, **7b** in 20–30 cm^3 of conc. H_2SO_4 and a solution of 2.42 g of KNO_3 (20 mmol) in 25 cm^3 of conc. H_2SO_4 were precooled to −18°C and mixed. The reaction mixture was kept at −18°C for 3 h, then at 4°C for 15 h and at room temperature for 3 h and poured on ice. The formed precipitate was filtered and washed thoroughly with saturated aqueous Na_2CO_3 and H_2O. The filtrate was extracted with 3×70 cm^3 of *Et*O*Ac*. The organic phase was washed successively with H_2O, two to three portions of saturated aqueous Na_2CO_3 (40 cm^3), dried, and concentrated to dryness. The solid residue was combined with the precipitate and purified by recrystallization from an appropriate solvent. The ^1H NMR spectra of the crude products showed a mixture of 8- and 9-nitro compounds.

7-Bromo-3-methyl-9-nitro-5-trifluoroacetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**3a**, $C_{12}H_9BrF_3N_3O_4$)

Compound **3a** was synthesized by nitration of **2a** and obtained by recrystallization of isomeric products mixture. Yield: 2.0 g (51%); mp 157–159°C (*tert*-butyl methyl ether); yellow crystals; IR: $\bar{\nu} = 3384$, 3328 (NH), 1711, 1697 (CO), 1537, 1345 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.22$ (d, $J = 6.8$ Hz, CH_3), 2.86 (m, CH), 3.73 (m, 1H, CH_2), 4.59 (m, 1H, CH_2), 7.76 (m, H-6), 8.41 (d, $J = 2.2$ Hz, H-8), 8.81 (bs, NH) ppm.

7-Bromo-9-nitro-5-trifluoroacetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**3b**, $C_{11}H_7BrF_3N_3O_4$)

Compound **3b** was synthesized by nitration of **2b** and obtained by recrystallization of isomeric products mixture.After separation of **3b** the organic filtrate was left for the following experiments. Yield: 1.37 g (36%); mp 150–152°C (*tert*-butyl methyl ether and petroleum ether); pale yellow crystals; IR: $\bar{\nu} = 3386$, 3329, 3230 (NH), 1709, 1690 (CO), 1539, 1345 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.55$–3.00 (bm, CH_2CO), 3.45–4.00 (bm, 1H, CH_2), 4.50–5.20 (bm, 1H, CH_2), 7.75 (m, H6), 8.36 (d, $J = 2.2$ Hz, H-8), 8.83 (bs, NH) ppm.

7-Bromo-5-formyl-3-methyl-9-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**8a**, $C_{11}H_{10}BrN_3O_4$)

Compound **8a** was synthesized by nitration of **7a** and obtained by recrystallization of isomeric products mixture. Yield: 2.0 g (61%); mp 209–211°C (toluene); pale yellow crystals; IR: $\bar{\nu} = 3265$ (NH), 1704, 1689, 1673 (CO), 1535, 1349 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$:*DMSO*-d_6, 1:1); two rotamers in a ratio of 86:14[a]: $\delta = 1.06$ (d, $J = 6.8$ Hz, CH_3), 2.97 (m, CH), 3.51 (m, 1H, CH_2), 4.34 (m, 1H, CH_2), 7.89 (d, $J = 2.2$ Hz, H-6), 8.14 (d, $J = 2.2$ Hz, H-8), 8.17 (s, CHO), [8.34 (s, CHO)], 9.72 (bs, NH) ppm.

[a] For **8a**–**8c** ^1H NMR peaks corresponding to the minor isomer are given in square brackets

7-Bromo-5-formyl-4-methyl-9-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one (**8b**, $C_{11}H_{10}BrN_3O_4$)

Compounds **8b** and **8c** were synthesized by nitration of **7b**. Fractional recrystallization of 2.5 g (77%) of isomeric products mixture from 120 cm^3 of *Me*OH:CH_2Cl_2 (1:10) gave **8c**. The filtrate was evaporated to 1/4 of its volume and cooled. Filtration gave 1.1 g of an inseparable mixture of **8c** and **8b**. After this the filtrate was concentrated to dryness. Recrystallization of a solid residue from 40 cm^3 of Et_2O:*Et*OAc (10:0.5) left **8b**. Yield: 0.4 g (12%); mp 171–173°C; yellow crystals; IR: $\bar{\nu} = 3380$ (NH), 1689 (CO), 1537, 1348 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$:*DMSO*-d_6, 1:1); two rotamers in a ratio of 85:15[a]: $\delta = 1.20$ (d, $J = 6.8$ Hz, CH_3), [1.28 (d, $J = 6.8$ Hz, CH_3)], 2.20–2.80 (m, CH_2), 4.97 (m, CH), 7.96 (d, $J = 2.2$ Hz, H-6), 8.14 (s, CHO), 8.24 (d, $J = 2.2$ Hz, H-8), [8.46 (s, CHO)], 9.79 (bs, NH) ppm.

7-Bromo-5-formyl-4-methyl-8-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one (**8c**, $C_{11}H_{10}BrN_3O_4$)

Yield: 0.5 g (15%); mp 251–253°C; deep yellow crystals; IR: $\bar{\nu} = 3182$ (NH), 1700, 1680 (CO), 1536, 1359 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$:*DMSO*-d_6, 1:1); two rotamers in a ratio of 87:13[a]: $\delta = 1.20$ (d, $J = 6.8$ Hz, CH_3), [1.28 (d, $J = 6.8$ Hz, CH_3)], 2.20–2.70 (m, CH_2), 4.93 (m, CH), 7.68 (s, 1H, H-6 or H-9), 7.75 (s, 1H, H-9 or H-6), 8.10 (s, CHO), [8.40 (s, CHO)], 10.21 (bs, NH) ppm.

*Synthesis of **4b**, **4c**, and **5** by Alkaline Hydrolysis of **2b** Nitration Products*

Method A. Nitration of **2b** (10 mmol) afforded 2.86 g (75%) of the mixture of **3b** and **3c**. After separation of **3b** (see above) the organic filtrate was concentrated to dryness and the resultant solid was dissolved in 50 cm^3 of *Et*OH. To this solution 5 cm^3 of 1 *N* NaOH was added under stirring. The reaction mixture suddenly became red. After stirring at room temperature for 30 min and cooling the formed precipitate of **4c** was filtered off and washed with H_2O until neutral washings. The ethanolic filtrate was evaporated to dryness and the residue was partitioned between 60 cm^3 of *Et*OAc and 30 cm^3 of H_2O. The aqueous phase was removed, the organic layer was dried, and concentrated to give **5**.

7-Bromo-8-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one (**4c**, $C_9H_8BrN_3O_3$)

Yield: 0.48 g (16.8%); mp 263–265°C (*Et*OH); orange needles; IR: $\bar{\nu} = 3384$, 3200 (NH), 1666 (CO), 1517 (NO_2) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.66$ (m, CH_2CO), 3.54 (m, CH_2), 7.05 (s, H-6), 7.54 (bs, NH), 7.87 (s, H-9), 9.72 (bs, NHCO) ppm.

3-(2-Amino-5-bromo-3-nitroanilino)propionic acid (**5**, $C_9H_{10}BrN_3O_4$)

Yield: 0.25 g (8%); mp 183–185°C (*i-Pr*OH:H_2O, 1:3); intense red crystals; IR: $\bar{\nu} = 3453$, 3411, 3356 (NH), 1707 (CO), 1523 (NO_2) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.57$ (t, $J = 6.8$ Hz, CH_2CO), 3.29 (bt, CH_2), 5.63 (bs, NH), 6.59 (d, $J = 2.0$ Hz, H-6), 7.26 (bs, NH_2), 7.39 (d, $J = 2.0$ Hz, H-4) ppm.

7-Bromo-9-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one (**4b**, $C_9H_8BrN_3O_3$)

Method B. Nitration of **2b** (10 mmol) afforded 2.7 g (71%) of the mixture of **3b**, **3c**. The residue obtained from concentration to dryness of the organic filtrate after separation of **3b** was dissolved in 50 cm^3 of *Et*OH and 3 cm^3 of NH_4OH were added. The reaction mixture became orange. After 5 min a precipitate began to form. Stirring was continued at room temperature for 1.5 h and then the mixture was cooled in a refrigerator. Filtration gave 0.5 g (17.5%) of **4c** (mp was identical with that of an authentic sample). The filtrate was evaporated to 1/2 of its volume, cooled, and filtration gave **4b**. Yield: 0.3 g (12%); mp 160–162°C (*Et*OH); orange brown crystals; IR: $\bar{\nu} = 3346$, 3194 (NH), 1689

(CO), 1530, 1356 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$:*DMSO*-d_6, 1:1): $\delta = 2.65$ (m, CH_2CO), 3.70 (m, CH_2), 6.14 (bs, NH), 7.34 (d, $J = 2.2$ Hz, H-6), 7.52 (d, $J = 2.2$ Hz, H-8), 9.19 (bs, NHCO) ppm.

7-Bromo-3-methyl-9-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**4a**, $C_{10}H_{10}BrN_3O_3$)

A solution of 0.51 g of **3a** (1.3 mmol) in 40 cm^3 of *Et*OH and 1 cm^3 of NH_4OH was stirred at room temperature for 1 h. The solution was concentrated to 1/2 of its volume, cooled, and the following filtration gave **4a**. Yield: 0.4 g (83%); mp 169–170°C (*Et*OH); orange friable needles; IR: $\bar{\nu} = 3366$, 3327, 3261 (NH), 1677 (CO), 1534, 1335 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.17$ (d, $J = 6.8$ Hz, CH_3), 2.83 (m, CH), 3.30–3.90 (m, CH_2), 4.07 (bs, NH), 7.22 (d, $J = 2.2$ Hz, H-6), 7.74 (d, $J = 2.2$ Hz, H-8), 8.99 (bs, NHCO) ppm.

Compound **4b** was synthesized from 0.5 g of **3b** (1.3 mmol) and 1 cm^3 of NH_4OH in analogy to **4a**. Yield: 0.3 g (63%); mp 162–164°C (*Et*OH); a mixed sample with authentic material did not show depression of the melting point. ^1H NMR spectra were identical.

7-Bromo-8-nitro-5-trifluoroacetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-one
(**3c**, $C_{11}H_7BrF_3N_3O_4$)

A solution of **4c** (0.4 g, 1.3 mmol) in 80 cm^3 of a mixture of dry 1,2-dichloroethane and dry *THF* (2:1) and 5.5 cm^3 of trifluoroacetic acid anhydride (39 mmol) was slowly heated till reflux for 30 min. TLC indicated complete consumption of the starting material. After evaporation of solvents the resulting residue was taken up in 50 cm^3 of $CHCl_3$, washed with H_2O, and then dried. Evaporation to dryness left crude **3c**. Yield: 0.3 g (60%); mp 171–173°C (*tert*-butyl methyl ether); grey brown crystals; IR: $\bar{\nu} = 3188$, 3109 (NH), 1701, 1682 (CO), 1547 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.55$–3.00 (bm, CH_2CO), 3.40–4.05 (bm, 1H, CH_2), 4.45–5.10 (bm, 1H, CH_2), 7.73 (s, 2H, H-6, H-9), 8.86 (bs, NH); in ($CDCl_3$:*DMSO*-d_6, 1:1): $\delta = 7.77$ (s, H-9), 7.94 (m, H-6) ppm.

*Acylation of **4b** with Trifluoroacetic Acid Anhydride* (*Synthesis of **3b***)

A solution of 0.4 g of **4b** (1.3 mmol) in 50 cm^3 of dry CH_2Cl_2 and 0.28 cm^3 (2.0 mmol) of trifluoroacetic acid anhydride was stirred at room temperature for 1 h. The reaction mixture was washed with H_2O, dried, and concentrated to give a solid. Crystallization from *tert*-butyl methyl ether afforded 0.4 g (80%) of pure **3b**, mp 153–155°C (mixed sample with authentic material did not show depression of the melting point).

3-(6-Bromo-4-nitro-2-trifluoromethylbenzimidazol-1-yl)propionic acid (**6b**, $C_{11}H_7BrF_3N_3O_4$)

A solution of **3b** (0.2 g, 0.5 mmol) in 25 cm^3 of *Ac*OH and 0.5 cm^3 of concentrated HCl was kept at room temperature for 24 h, then 200 cm^3 of H_2O were added. The reaction mixture was extracted with 3×30 cm^3 of *EtOAc*, the organic phase was separated, washed with H_2O, dried, and concentrated. The solid residue was purified by recrystallization. Yield: 0.15 g (75%); mp 159–161°C (*Me*OH); yellowish crystals; IR: $\bar{\nu} = 1708$ (CO), 1539 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$:*DMSO*-d_6, 8:1): $\delta = 2.85$ (t, $J = 6.8$ Hz, CH_2CO), 4.69 (t, $J = 6.8$ Hz, CH_2N), 8.27 (s, 2H, H-5, H-7); in ($CDCl_3$:*DMSO*-d_6:C_6D_6, 8:1:2): $\delta = 8.06$ (d, $J = 2.2$ Hz, 1H, H-5 or H-7), 8.16 (d, $J = 2.2$ Hz, 1H, H-7 or H-5) ppm.

3-(6-Bromo-5-nitro-2-trifluoromethylbenzimidazol-1-yl)propionic acid (**6c**, $C_{11}H_7BrF_3N_3O_4$)

Compound **6c** was synthesized from 0.2 g of **3c** (0.5 mmol) in analogy to **6b**. Yield: 0.1 g (50%); mp 218–220°C (*Me*OH); yellowish crystals; IR: $\bar{\nu} = 1710$ (CO), 1542 (NO_2) cm^{-1}; ^1H NMR

($CDCl_3$:*DMSO*-d_6, 1:1): $\delta = 2.84$ (t, $J = 6.8$ Hz, CH_2CO), 4.69 (t, $J = 6.8$ Hz, CH_2), 8.38 (s, 1H, H-4 or H-7), 8.40 (s, 1H, H-7 or H-4) ppm.

General Procedure for the Synthesis of Tetrahydroimidazo[1,5,4-e,f][1,5]benzodiazepine-2(1H)-thiones

A solution of 5 mmol of **4a** or **8a** in 60 cm^3 of dry *THF* was added to a stirred suspension of 1.52 g of $LiAlH_4$ (40 mmol) in 50 cm^3 of dry *THF* which had been refluxed for 0.5 h. The reaction mixture was heated at reflux for 1 h, cooled, and quenched by sequential addition of 1.5 cm^3 of H_2O, 3 cm^3 of 15% NaOH aqueous solution, and 1.5 cm^3 of H_2O. The solid was removed by filtration, the organic solution concentrated, and the resultant dark residue was dissolved in 30 cm^3 of *Me*OH. To this solution 0.8 cm^3 (1.0 g, 13 mmol) of CS_2 were added under N_2. The reaction mixture was allowed to stir at ambient temperature for 24 h. Removal of the solvent left a solid residue. Subjection of the residue to dry column vacuum chromatography (using the $C_6H_6/ClCH_2CH_2Cl$ system for gradient elution) gave **11** or **12**.

9-Bromo-5-methyl-4,5,6,7-tetrahydroimidazo[1,5,4-e,f][1,5]benzodiazepine-2(1H)-thione (**11**, $C_{11}H_{12}BrN_3S$)

Yield: 0.52 g (35%); mp 241–243°C (*Me*OH/Et_2O); sand-coloured crystals; IR: $\bar{\nu} = 3378$, 3291, 3146 (NH), 1622 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.02$ (d, $J = 6.8$ Hz, CH_3), 1.85–2.40 (m, CH), 2.90–3.50 (m, CH_2), 3.78 (dd, $J = 8.8$ and 13.6 Hz, 1H, CH_2NCS), 4.23 (dd, $J = 3.2$ and 13.6 Hz, 1H, CH_2NCS), 6.35 (bs, NH), 6.53 (d, $J = 1.8$ Hz, H-8), 6.62 (d, $J = 1.8$ Hz, H-10), 12.71 (bs, NHCS) ppm.

9-Bromo-5,7-dimethyl-4,5,6,7-tetrahydroimidazo[1,5,4-e,f][1,5]benzodiazepine-2(1H)-thione (**12**, $C_{12}H_{14}BrN_3S$)

Yield: 0.48 g (31%); mp 230–232°C (*i-Pr*OH); sand-coloured crystals; IR: $\bar{\nu} = 3151$ (NH), 1613 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.10$ (d, $J = 7.0$ Hz, CH_3), 2.42 (m, CH), 3.00–3.45 (m, CH_2), 3.04 (s, CH_3N), 3.85 (dd, $J = 8.8$ and 13.6 Hz, 1H, CH_2NCS), 4.52 (dd, $J = 3.0$ and 13.6 Hz, 1H, CH_2NCS), 6.55 (d, $J = 1.8$ Hz, H-8), 6.89 (d, $J = 1.8$ Hz, H-10), 11.44 (bs, NH) ppm.

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