ХИМИЯ ГЕТЕРОЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ. — 2000. — № 6. — С. 799—805

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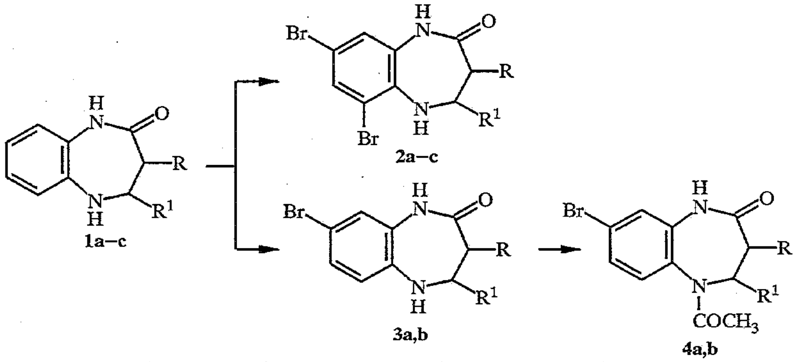
AROMATIC RING BROMINATION OF TETRAHYDRO-1,5-BENZODIAZEPIN-2-ONES

Novel mono- or dibromo-substituted tetrahydro-1,5-benzodiazepinones were obtained by direct bromination of the corresponding 2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-ones and 5-N-alkyl(or formyl) derivatives with bromine. Substituent effects and the orientation of the entering groups in the bromination reaction are discussed.

Keywords: tetrahydro-1,5-benzodiazepin-2-ones, bromination.

To our knowledge, aromatic ring substituents in tetrahydro-1,5-benzodiazepinones can be generally incorporated *prior* to the synthesis of the desired heterocycle [1, 2], and when this is not convenient the desired targets can be attained *via* a direct electrophilic aromatic substitution. Unlike dihydro-1,5-benzodiazepinones [3—5], the literature provides no data concerning functionalization reactions of the aromatic ring in tetrahydrobenzodiazepinones [6]. Therefore it was of great interest to study the directions of these reactions and to evaluate the orientation effects. On the other hand, we required as intermediates the novel nitro substituted compounds derived from 7 (or 8)-halotetrahydrobenzodiazepinones which are useful for the synthesis of a *peri*-fused tricyclic heterosystem. We describe herein the preparation of new mono- and dibrominated tetrahydro-1,5-benzodiazepin-2-ones.

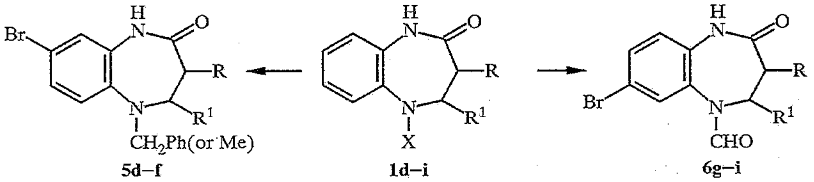
Scheme 1



1 a R = R^1 = H; **b** R = Me, R^1 = H; **c** R = H, R^1 = Me
4 a R = R^1 = H; **b** R = Me, R^1 = H

We started with tetrahydro-1,5-benzodiazepin-2-one **1a** and 3(or 4)-methyl homologues **1b,c,** which were prepared according to the procedures described previously [7]. Treatment of compounds **1a—c** with a large excess of bromine in the mixture of acetic acid and concentrated sulfuric acid at ambient temperature led to 6,8-dibromo derivatives **2a—c** (Scheme 1). We were particularly interested in obtaining the monobromo-substituted derivatives as key intermediates for synthetic route to a fused system. In this context, the reaction of **1a** with bromine was examined in a more detailed way. Under the same conditions, using two molar equivalents of the brominating agent, dibromo-substituted product **2a** was obtained with a smaller yield, while the reaction of this compound with one molar equivalent of bromine afforded a mixture of 8-mono and 6,8-dibromo-substituted derivatives **2a** and **3a**. It was also shown that the both brominated derivatives **2a** and **3a** were obtained from **Ia** by the treatment with bromine in chloroform or with dioxane dibromide, the crude mixtures of products being purified by fractional crystallization. The reaction of compound **Ib** with bromine in acetic acid or chloroform led to the mixture of brominated products **2b** and **3b**, which were not separated. Acetylation of the preceding mixture gave **4b** along with unreacted 6,8-dibromide **2b** bearing a bulky substituent in position 6. Compound **3a** was converted to the expected product **4a** by the reaction with acetic anhydride.

Scheme 2



	X	R	R^1		X	R	R^1
1d	CH_2Ph	H	H	**1g**	CHO	H	H
1e	Me	H	H	**1h**	CHO	Me	H
1f	Me	Me	H	**1i**	CHO	H	Me

On the other hand, the bromination of 5-N-benzyl derivative **1d** [8] led to 8-monobromide **5d** as the main isolated product (Scheme 2). The reaction of 5-N-methyl derivatives **1e,f** [9] with excess of bromine afforded 8-monobrominated products **5e,f** which were isolated with poor yields. Monitoring the progress of the reactions by TLC showed the formation of several products. It is quite possible that these reactions are accompanied by substitution in the aromatic ring of benzyl substituent (compound **1d**) or in the diazepine nucleus and methyl substituent in $C_{(3)}$ position (compounds **1e,f**). Such a direction of the reaction was observed for the bromination of dihydro-1,5-benzodiazepinone derivatives [4, 5]. Compound **5e** was also prepared from **3a** by alkylation with iodomethane.

However, we were interested in preparing compounds possessing a novel functionality on the aromatic ring, especially at position 7. Therefore, we selected the 5-N-formyl derivatives **1g–i** as starting materials [10]. Using two molar equivalents of bromine in the mixture of acetic acid and concentrated sulfuric acid at room temperature, bromination of **1g–i** gave exclusively 7-bromo- substituted products **6g–i**.

The position of the bromo-substituent in monobrominated products **3a,b** was assigned by analysis of the ^{1}H NMR spectra (see Table 1). The presence of doublets with coupling constants of 8.6 Hz between the two *ortho* protons at 6.55 ppm ($CDCl_3$) or at 6.62 ppm (DMSO-d_6) is in favor of 6-H protons. These data allow one to state that the bromo-substituent is in position 8 in these compounds. The structural identification of brominated 5-formyl derivatives **6g—i** was carried out by comparison of their ^{1}H NMR spectra with those of 5-N-acetyl derivatives **4a,b**. The spectra of aldehydes **6g—i** indicate a mixture of *E*- and *Z*-forms with one form dominating (87—95%). In DMSO-d$_6$ solution the signals of NH and CH$_3$ group protons were also affected by the *E*/*Z* isomerism.

In the 1,5-benzodiazepin-2-one system the aromatic ring is activated both by the acylamino group and nitrogen N(5) *ortho* to the lactam moiety and, not surprisingly, the substitution is directed to this ring. The orientation of the entering groups is strongly influenced by competing substituent effects of these two groups. The greater propensity for lone pair delocalization by N(5) atom accounts for the 8-mono or 6,8-dibromination. In addition, the incorporation of benzylic or methyl substituents into N(5) did not change the orientation of the entering group in the bromination of **1d—f**. It was previously reported that 2-phenyl-1,4-benzodiazepin-5(4H)-one was chlorinated using *tert*-butyl hypochlorite exclusively in the fused benzene ring in positions 7 and 9, i. e., *para* and *ortho* to the activating heterocyclic amino group N(1) [11]. Thus, on the basis of our data and reported results the orientation of the entering bromo substituent in the bromination of unsubstituted tetrahydro-1,5-benzodiazepinones **1a—c** appears to follow the usual substituent effects for electrophilic aromatic substitution and differs from the 2,3-dihydro-1,5- and 1,3-dihydro-1,4-benzodiazepin-2-one systems [3—5, 12, 13].

In the case of 5-N-formylated derivatives **1g—i**, electrophilic substitution with the formation of 7-bromo-substituted derivatives **6g—i** was not unexpected, and the dominating *para>ortho* directing activating effect of the acylamino group (lactamic) was accomplished. It was also reported that nitration of 5-acetyl-4-methyltetrahydro-1,5-benzodiazepin-2-one led to a 7-nitro- substituted derivative [14], and the reaction of 4-alkyltetrahydro-1,4-benzodiazepin-2,5-diones with excess of bromine resulted also in the corresponding 7-bromo derivatives [15, 16]. In this case, the substitution occures at C(7), since the acylamino substituent activates benzene ring moderately.

In view of these results, it could be summarized that the novel bromo derivatives of tetrahydro-1,5-benzodiazepin-2-ones were obtained by direct electrophilic bromination of the aromatic ring in this heterocyclic system. The orientation of the entering groups is strongly influenced by substituent effects. The spectroscopic as well as physical and analytical data of previously unreported compounds are summarized in Tables 1 and 2.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Hitachi R-22 spectrometer operating at 90 MHz (35 °C). Chemical shifts (δ) are reported in ppm from TMS. IR spectra were recorded for KBr pellets on a Specord 71 IR spectrophotometer. TLC was performed on Silufol UV-254 silica gel plates in the system chloroform—ethyl acetate—methanol, 14 : 7 : 1. Melting points were determined in open capillary tubes and were uncorrected.

6,8-Dibromo-3-R-4-R^1-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (2a—c). General procedure. To a precooled (in ice bath) and stirred solution of the corresponding compound **1a—c** (10 mmol) in 15 ml of acetic acid and 1.5 ml of concentrated sulfuric acid, a solution of bromine (2.1 ml, 40 mmol) in the same solvent (5 ml) were added slowly dropwise. The mixture was stirred at ambient temperature for 4 h and poured into water (approximately 400 ml) with ice.

Table 1

IR and ^{1}H NMR data for compounds 2a—c, 3a, b, 4a, b, 5d—f, 6g—i

Compound	IR, cm^{-1}	^{1}H NMR[*] δ (ppm), *J* (Hz)
2a	1700, 1670 (CO), 3350—3180 (NH)	2.54 (2H, m, CH_2CO), 3.52 (2H, m, CH_2N), 5.43 (1H, bs, NH), 7.10 (1H, d, $^4J = 2.2$, 9-H), 7.37 (1H, d, $^4J = 2.2$, 7-H), 9.60 (1H, s, NHCO)
2b	1670 (CO), 3360—3200 (NH)	0.98 (3H, d, CH_3), 2.65 (1H, m, CH), 3.06—3.60 (2H, m, CH_2), 5.35 (1H, bs, NH), 7.10 (1H, d, $^4J = 2.2$, 9-H), 7.38 (1H, d, $^4J = 2.2$, 7-H), 9.59 (1H, s, NHCO)
2c	1670 (CO), 3390—3190 (NH)	1.25 (3H, d, CH_3), 2.30 (1H, dd, $^2J = 13.0$, $^3J = 7.4$, CH_2), 2.47 (1H, dd, $^3J = 4.0$, CH_2), 4.03 (1H, m, CH), 4.76 (1H, bs, NH), 7.10 (1H, d, $^4J = 2.2$, 9-H), 7.46 (1H, d, $^4J = 2.2$, 7-H), 9.72 (1H, s, NHCO)
3a	1655 (CO), 3390—3190 (NH)	2.71 (2H, m, CH_2CO), 2.74 (1H, bs, NH), 3.63 (2H, m, CH_2N), 6.55 (1H, d, $^3J = 8.6$, 6-H), 6.96 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 7-H), 7.09 (1H, d, $^4J = 2.2$, 9-H), 8.23 (1H, s, NHCO)
3b		0.98 (3H, d, CH_3), 2.65 (1H, m, CH), 3.06—3.60 (2H, m, CH_2), 5.74 (1H, bs, NH), 6.62 (1H, d, $^3J = 8.6$, 6-H), 6.91 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 7-H), 6.96 (1H, d, $^4J = 2.2$, 9-H), 9.38 (1H, s, NHCO)
4a	1690, 1650 (CO), 3170 (NH)	1.85 (3H, s, CH_3), 2.35—2.80 (2H, m, CH_2CO), 3.10—5.10 (2H, m, CH_2), 7.05 (1H, d, $^3J = 8.6$, 6-H), 7.33—7.41 (2H, m, 7-H, 9-H), 8.55 (1H, s, NH)
4b	1680, 1650 (CO), 3190—3120 (NH)	0.96 (3H, d, CH_3), 1.66 (3H, s, CH_3CO), 2.69 (1H, m, CH), 3.26—3.60 (1H, m, CH_2), 4.09—4.49 (1H, m, CH_2), 7.15—7.42 (3H, m, Ar)[*], 9.81 (1H, s, NH)
5d	1680 (CO), 3175 (NH)	2.52 (2H, bt, CH_2CO), 3.45 (2H, bt, CH_2N), 4.27 (2H, s, CH_2Ar), 6.88 (1H, d, $^3J = 8.5$, 6-H), 6.95—7.15 (2H, m, 7-H, 9-H), 7.25 (5H, m, Ar), 8.04 (1H, s, NH)
5e	1660 (CO), 3175 (NH)	2.37 (2H, m, CH_2CO), 2.76 (3H, s, CH_3), 3.41 (2H, m, CH_2N), 7.00 (1H, d, $^3J = 8.6$, 6-H), 7.11 (1H, d, $^4J = 2.2$, 9-H), 7.29 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 7-H), 9.64 (1H, s, NH)
5f	1695 (CO), 3180 (NH)	0.97 (3H, d, CH_3), 2.60--3.93 (3H, m, CH_2CH), 2.73 (3H, s, CH_3N), 7.00 (1H, d, $^3J = 8.6$, 6-H), 7.05 (1H, d, $^4J = 2.2$, 9-H), 7.26 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 7-H), 9.60 (1H, s, NH)
6g	1680, 1650 (CO), 3195--3120 (NH)	2.57 (2H, m, CH_2CO), 3.97 (2H, m, CH_2N), 7.09 (1H, d, $^3J = 8.6$, 9-H), 7.55 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 8-H), 7.60 (1H, d, $^4J = 2.2$, 6-H), 8.25[*3] and 8.36[*2] (1H, s, CHO), 9.78[*2] and 9.90[*3] (1H, s, NH)
6h	1700, 1650 (CO), 3195—3120 (NH)	1.14 (3H, d, CH_3), 2.87 (1H, m, CH), 3.59 (1H, ddd, $^2J = 13.0$, $^3J = 5.1$, $^4J = 1.0$, CH_2), 4.20 (1H, dd, $^2J = 13.0$, $^3J = 12.9$, CH_2), 7.04 (1H, d, $^3J = 8.6$, 9-H), 7.28 (1H, d, $^4J = 2.2$, 6-H), 7.41 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 8-H), 8.14[*3] and 8.31[*2] (1H, s, CHO), 9.65 (1H, s, NH)
6i	1685, 1650 (CO), 3190—3120 (NH)	1.15[*3] and 1.20[*2] (3H, d, CH_3), 2.30—2.58 (2H, m, CH_2), 4.84 (1H, m, CH), 7.07 (1H, d, $^3J = 8.6$, 9-H), 7.57 (1H, d, $^4J = 2.2$, 6-H), 7.62 (1H, dd, $^3J = 8.6$, $^4J = 2.2$, 8-H), 8.08[*3] and 8.40[*2] (1H, s, CHO), 9.79[*2] and 9.92[*3] (1H, s, NH)

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[*] Solvents: compound **2a—c**, **3b**, **4b**, **5e,f**, **6g—i** in DMSO-d_6; **6h** in $CDCl_3$—DMSO-d_6, 9 : 1; **3a**, **4a**, **5d** in $CDCl_3$. **4b** (in $CDCl_3$) 7.05 (1H, d, $^3J = 8.6$, 6-H), 7.26—7.42 (2H, m, 7-H, 9-H).

[*2] The minor form.

[*3] The major form.

Table 2

Physical and analytical data of compounds 2a–c, 3a, 4a,b, 5d–f and 6g–i

Compound	Molecular formula (M)	Found, % / Calculated, %				Mp, °C (solvent)	Yield, %
		C	H	N	Br		
2a	$C_9H_8Br_2N_2O$ (319.99)	33.67 33.78	2.82 2.52	8.82 8.75	50.15 49.94	232—234 (PrOH)	55
2b	$C_{10}H_{10}Br_2N_2O$ (334.02)	36.04 35.96	2.98 3.02	8.36 8.39	47.93 47.85	239—241 (PrOH)	54
2c	$C_{10}H_{10}Br_2N_2O$ (334.02)	35.98 35.96	3.23 3.03	8.46 8.39	47.36 47.85	190—191 (EtOH)	61
3a	$C_9H_9BrN_2O$ (241.09)	44.70 44.84	3.63 3.76	11.65 11.62	32.64 33.14	170—173 (Benzene)	—
4a	$C_{11}H_{11}BrN_2O_2$ (283.13)	46.85 46.66	4.13 3.92	10.05 9.89	28.59 28.22	221—223 (EtOAc)	68
4b	$C_{12}H_{13}BrN_2O_2$ (297.16)	48.84 48.50	4.68 4.41	9.50 9.43	27.37 26.89	197—199 (EtOAc—Et_2O)	—
5d	$C_{16}H_{15}BrN_2O$ (331.22)	57.94 58.02	4.63 4.56	8.63 8.46	23.70 24.13	158—160 (Benzene)	34
5e	$C_{10}H_{11}BrN_2O$ (255.12)	47.37 47.08	4.61 4.35	11.09 10.98	31.00 31.32	167—170 (Benzene—Et_2O)	62
5f	$C_{11}H_{13}BrN_2O$ (269.15)	50.34 49.09	5.13 4.87	10.10 10.41	29.31 29.69	209—212 (Benzene—Et_2O)	31
6g	$C_{10}H_9BrN_2O_2$ (269.10)	44.84 44.63	3.61 3.37	10.25 10.41	30.13 29.69	148—150 (EtOAc)	55
6h	$C_{11}H_{11}BrN_2O_2$ (283.13)	46.75 46.66	4.17 3.92	10.00 9.89	28.72 28.22	203—205 (EtOAc)	57
6i	$C_{11}H_{11}BrN_2O_2$ (283.13)	46.39 46.66	3.73 3.92	10.12 9.89	28.67 28.22	231—233 (EtOAc)	65

After neutralizing with NH_4OH the resultant precipitate was filtered off, washed with water, and crude products **2a**—**c** were crystallized from an appropriate solvent.

According to the procedure described above, the reaction of compound **1a** (1.6 g, 10 mmol) with bromine (1.0 ml, 20 mmol) gave 1.2 g (38%) of **2a** as white crystals. M.p. was identical with that of an authentic sample.

Synthesis of 6,8-dibromo- and 8-bromo-3-R-4-R^1-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (2a and 3a). A. A solution of bromine (1.0 ml, 20 mmol) in acetic acid (5 ml) was added dropwise to a solution of compound **1a** (3.2 g, 20 mmol) in a mixture of acetic acid (30 ml) and sulfuric acid (3 ml), and stirred at room temperature for 4 h. The reaction mixture was poured into water with crushed ice, neutralized with NH_4OH and extracted with BuOH (100 ml). Evaporation of the solvent in *vacuo* afforded a solid residue which was crystallized from PrOH to give 0.7 g (11%) of dibromo product **2a** identical with an authentic sample. The filtrate was concentrated in *vacuo* and a solid residue was obtained. Crystallization of this crude residue from benzene gave 1.0 g (21%) of monobromo product **3a** as white crystals.

B. A solution of bromine (1.0 ml, 20 mmol) in chloroform (100 ml) was added to a stirred solution of compound **1a** (3.2 g, 20 mmol) in the same solvent (10 ml). The reaction mixture was stirred at room temperature for 5 h. The precipitated solid was collected by filtration, washed with saturated aqueous Na_2CO_3 solution and water. The organic filtrate was washed with the same Na_2CO_3 solution (3×30 ml) and water. After drying (anhydrous $MgSO_4$), chloroform was removed and a solid residue combined with the precipitate was crystallized from PrOH to give 1.9 g (30%) of **2a**. The filtrate was concentrated to give white solid crystals. The crystallization from benzene gave 0.5 g (11%) of compound **3a**.

C. The same procedure as for method **B**, except that the reaction of compound 1a with bromine was carried out at 5 °C for 4 h and products **2a** (22%) and **3a** (31%) were isolated.

D. A solution of compound **1a** (3.2 g, 20 mmol) in dioxane (30 ml) and 1.1 g (20 mmol) of KOH in water (4 ml) was treated dropwise with bromine (1.0 ml, 20 mmol) in 50 ml of dioxane under stirring. After complete addition the mixture was stirred at room temperature for 0.5 h. The precipitated solid was collected by filtration, washed with saturated aqueous Na_2CO_3 solution (2×20 ml) and water. Evaporation of the filtrate gave a solid residue which was dissolved in 1,2-dichloroethane (100 ml). The organic solution was washed with the same Na_2CO_3 solution (3×30 ml), then with water and dried. Evaporation of the solvent in *vacuo* gave a white solid residue. The latter was combined with precipitate, recrystallized as described above in method **B** and gave 1.4 g (22%) of **2a** and 1.3 g (27%) of **3a**.

In all experiments, products **2a** and **3a** were identified by TLC, and mixed samples compounds with authentic did not show depression of the melting point.

Synthesis of 6,8-dibromo- and 8-bromo-3-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (2b and 3b). A. To a solution of compound **1b** (2.64 g, 15 mmol) in 300 ml of chloroform, a solution of bromine (1.25 ml, 25 mmol) in the same solvent (10 ml) was added dropwise at a temperature of 10 °C, and the mixture was stirred at room temperature for 4 h. The precipitate was filtered off. Further, the procedure described in method **B** gave a solid residue. The precipitate and residue were combined (2.0 g) and crystallized subsequently from MeCN, 1,2-dichloroethane or *i*-PrOH to give a mixture (1.63 g) of products **2b** and **3b** which were not separated as individual compounds. The ^1H NMR spectrum of this mixture indicated the presence of bromides **2b** and **3b** (approximate ratio 2 : 1).

B. To a stirred solution of compound **1b** (2.64 g, 15 mmol) in acetic acid (30 ml), a solution of bromine (1.25 ml, 25 mmol) in the same solvent (5 ml) was added dropwise. After stirring at room temperature for 3 h and following the procedure described in the general procedure for preparation of **2a**—**c**, a mixture (1.3 g) of bromides **2b** and **3b** was obtained.

5-Acetyl-8-bromo-3-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (4b). A solution of 1.63 g of a mixture of products **2b** and **3b** in dry 1,2-dichloroethane (80 ml) and 1.0 ml (10 mmol) of acetic anhydride was refluxed for 6 h. After cooling, the solution was washed with water and dried. TLC indicated a complete consumption of one of the components from the starting mixture and the appearance of a new spot, while the other component remained unchanged. Evaporation of the solvent *in vacuo* afforded crude solid products. Crystallization from EtOAc gave 0.9 g of unchanged **2b** identical with an authentic sample. The filtrate was concentrated and treated with Et_2O to give 0.35 g of compound **4b**.

5-Acetyl-8-bromo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (4a). According to the procedure described for the synthesis of **4b**, the reaction of compound **3a** (0.3 g, 1.24 mmol) with acetic anhydride (0.2 ml, 2.1 mmol) gave 0.24 g of **4a** as white crystals.

5-Benzyl-8-bromo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (5d). To a solution of **1d** (2.5 g, 10 mmol) in 30 ml of acetic acid, a solution of bromine (1.0 ml, 20 mmol) in the same solvent (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and poured into water (450 ml) with crushed ice. After neutralizing with NH_4OH, the mixture was extracted repeatedly with EtOAc (120 ml). The extract was washed with brine and dried. Evaporation of the solvent afforded a solid residue of the crude product. Crystallization from benzene gave 0.88 g of bromo derivative **5d** as gray crystals. After concentration of benzenic filtrate, 0.5 g of unreacted **1d** were obtained.

8-Bromo-5-methyl-3-R-4-R^1-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (5e,f). The reaction of **1e,f** (10 mmol) with bromine was accomplished according to the general procedure for the preparation of **2a—c**. Compounds **5e,f** were isolated with 27 and 31% yield, respectively.

8-Bromo-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (5e). A well stirred mixture of compound **3a** (2.75 g, 11.4 mmol), $NaHCO_3$ (1.43 g, 17 mmol) and iodomethane (2.8 ml, 45 mmol) in methanol (50 ml) was refluxed for 14 h. After cooling the solid was collected and filtrate was concentrated to a thick residue which was dissolved in 60 ml of 1,2-dichloroethane. The organic solution was washed with water (2×30 ml) and dried. Evaporation of the solvent left a crude solid residue. Crystallization gave 1.8 g of N-methyl derivative **5e**. The mixed sample with compound **5e** obtained by a different way did not show the depression of melting point. The IR and ^1H NMR spectra were identical.

7-Bromo-5-formyl-3-R-4-R^1-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (6g—i). General procedure. A solution of bromine (1.0 ml, 20 mmol) in 5 ml of acetic acid was added dropwise to a stirred solution of **1g—i** (10 mmol) in 30 ml of acetic acid and 1 ml of concentrated sulfuric acid. The mixture was stirred at room temperature for 4 h, then poured onto 300 ml of water with crushed ice and extracted several times (3×40 ml) with EtOAc. The extract was washed subsequently with saturated aqueous Na_2CO_3 solution, aqueous $Na_2S_2O_3 \cdot 5H_2O$ solution, water and dried. Evaporation of the solvent afforded a solid residue of crude products. Crystallization from appropriate solvents gave monobromo derivatives **6g—i** as white crystals.

We are grateful to the Foundation of Lithuanian Science and Studies for financial support.

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Received March 15, 2000