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Benzodiazepines with Psychotropic Activity. 7.[1] Synthesis and Biological Action of 4-Amino-1,5-benzodiazepines

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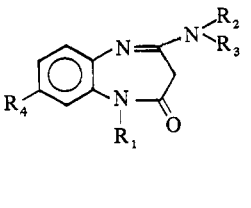
This paper gives a description of the syntheses of substituted 4-amino-1,5-benzodiazepines **1**. In addition, the possibility is discussed that due to corresponding structural features the 1,5- and 1,4-benzodiazepines (see **6**, **7**) exhibit similar effects on the central nervous system (CNS). Pharmacological data are given for **1**. The biological properties of some particularly active compounds (*e.g.*, **1c** and **1n**) are dealt with in detail.

Diazepam **2**[2] and **3a**†[,3,4] on the one hand and medazepam **4**[2] and benzodiazepines of type **5**[5] on the other hand show a partly analogous action in the animal experiment in respect to their effect on the CNS. Apparently the two structural types **6** and **7** have a similar profile of pharmacological action. Compounds of structure **1** were of interest in this



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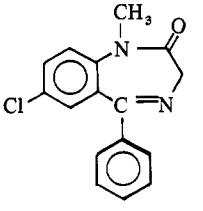

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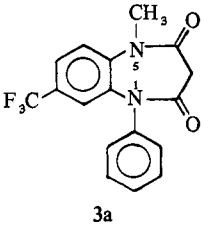

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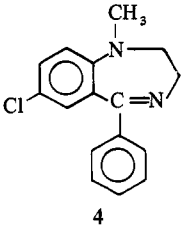

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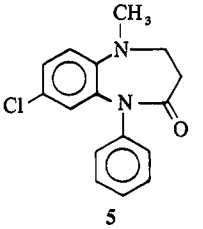

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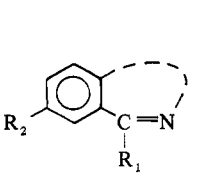

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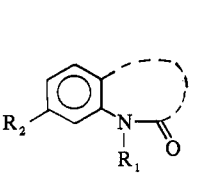

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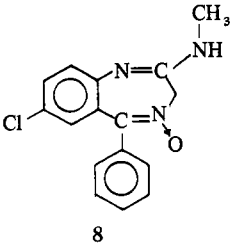

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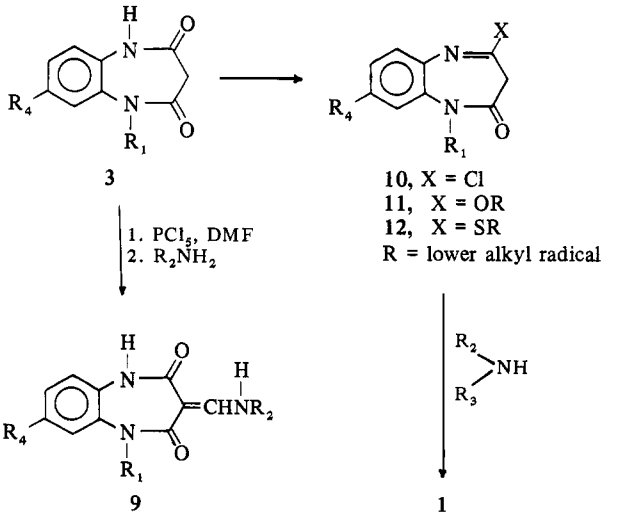
context; they exhibit a structural relationship to chlordiazepoxide[2] **8** and can be expected to have the ability to form water-soluble salts, which appears favorable for pharmacological reasons.

Chemistry. 1,5-Benzodiazepine-2,4 diones **3**[4] could be converted to 3-aminomethylidene-1,5-benzodiazepines **9**[6] by means of phosphorus pentachloride and alkylamines in DMF. A high yield of **9** was obtained only if the alkylamine was added to the reaction mixture of phosphorus pentachloride, DMF, and **3** after several hours. If the alkylamine was added after only a few minutes, the amidine **1** in a mixture of **3** and **9** was obtained. A high yield of **1** was obtained in dioxane and also to some degree in other inert solvent. The imino chloride **10**[7-9] probably occurs as an intermediate but was not isolated. The conversion of **3** to **1** could also be directed through the iminoether **11** or the imino sulfide **12**, which could relatively smoothly be converted to **1** by means of the amine as was expected.[10,11] In order to trace structure-activity relationships we have synthesized a series of these compounds[12] as shown in Scheme

Scheme I

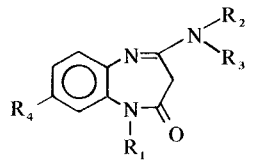


I. A selection is given together with pharmacological data for guidance (Table I).

Compounds **3**,[4] **5**,[5] **9**,[6] **11**, and **12** have previously been described; we synthesized **3** with $R_4 = NO_2$ by way of oxi-

†Compound **3a** has been designated ORF 8063 in earlier publications. In ref 4 it appeared as **1n**.

Table I. Compounds of Structure **1**, Their Relevant Chemical Data, and Some Pharmacological Properties in Comparison with Chlordiazepoxide



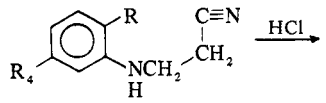
	R_1	R_2	R_3	R_4	Method[k]	Recrystn solvents	Yield, %	Mp, °C dec	Formula	Mol wt	Analyses	Pharmacology[a] Ataxia,[b] ED_{50}, mg/kg	Lying on side,[c] ED_{50}, mg/kg	Electroshock,[d] ED_{50}, mg/kg	Lethality, LD_{50},[e] mg/kg
1a	C_6H_5	H	H	Cl	A	MeOH–*i*-Pr_2O	51	242–243	$C_{15}H_{12}ClN_3O$	285.6	C, H, Cl; N[f]	53	880	32	990
1b	C_6H_5	H	H	CF_3	A	CH_2Cl_2–*i*-Pr_2O	54	227–228	$C_{16}H_{12}F_3N_3O$	319.3	C, H, N, F	126	623	27	2066
1c[l]	C_6H_5	H	H	NO_2	A	DMF	68	238–240	$C_{16}H_{16}N_4O_6S$	392.4	C, H, N	11	2600	29	3200
1d	C_6H_5	H	H	Br	A	CH_2Cl_2–Et_2O	49	248–249 276–278[l]	$C_{15}H_{12}BrN_3O$	330.2	C, H, N; Br[g]	17	580	37	1300
1e	C_6H_5	H	H	F	A	CH_2Cl_2–Et_2O	43	222–224	$C_{15}H_{12}FN_3O$	269.3	H, N, F; C[h]	105	>807	160	>807
1f	*o*-F-C_6H_4	H	H	Cl	A	EtOAc	35	258–259	$C_{15}H_{11}ClFN_3O$	303.8	C, H, N	76	>910	165	>910
1g	*o*-Cl-C_6H_4	H	H	Cl	A	CH_2Cl_2–Et_2O	38	260–262	$C_{15}H_{11}Cl_2N_3O$	320.2	C, H, N, Cl	270	1650	100	>2880
1h	C_6H_5	H	*i*-C_3H_7	CF_3	A	*i*-Pr_2O	42	215–217	$C_{19}H_{18}F_3N_3O$	361.4	C, H, N	210	1900	88	>3250
1i	C_6H_5	H	*t*-C_4H_9	Cl	A	MeOH	88	275	$C_{19}H_{20}ClN_3O$	341.9	C, H, N, Cl	1750	>3080	>342	>3080
1j	C_6H_5	H	CH_3	NO_2	C	CH_2Cl_2–*i*-Pr_2O	75	217–219	$C_{16}H_{14}N_4O_3$	310.3	C, N; H[i]	104	>2790	270	>2790
1k	C_6H_5	H	CH_3	CF_3	B	CH_2Cl_2–*i*-Pr_2O	92	201–203	$C_{17}H_{14}F_3N_3O$	333.3	C, H, N, F	160	660	47	>2700
1l	C_6H_5	H	$CH_2CH{=}CH_2$	Cl	A	THF–*i*-Pr_2O	48	173–176	$C_{18}H_{16}ClN_3O$	325.8	C, H, N, Cl	185	>975	185	>975
1m	C_6H_5	CH_3	CH_3	CF_3	A	*i*-Pr_2O	63	154–155	$C_{18}H_{16}F_3N_3O$	347.4	C, H, N, F	130	600	41	1200
1n	C_6H_5	CH_3	CH_3	NO_2	C	CH_2Cl_2–*i*-Pr_2O	80	219–220	$C_{17}H_{16}N_4O_3$	324.4	C, H, N	21	>2316	219	>2316
1o	C_6H_5	H	CH_3	Cl	C	CH_2Cl_2–*i*-Pr_2O	68	217–220	$C_{16}H_{14}ClN_3O$	299.8	C, H, N	23	890	41	>1550
1p	C_6H_5	H	C_2H_5	CF_3	A	*i*-Pr_2O	43	181–183	$C_{18}H_{16}F_3N_3O$	347.4	C, H, N	50	590	44	>3123
1q	C_6H_5	H	$(CH_2)_2OH$	NO_2	B	MeOH	67	191–193	$C_{17}H_{16}N_4O_4$	340.4	C, H; N[j]	140	>3060	>340	>3060
1r	C_6H_5	H	$(CH_2)_3OC_2H_5$	Cl	A	Et_2O	76	169–170	$C_{20}H_{22}ClN_3O_2$	371.9	C, H, N, Cl	230	>3200	>360	>3200
1s[m]	H	H	H	Cl	*n*			274–277	$C_9H_8ClN_3O$	209.6	C, H, Cl, N				
1t	C_6H_5	H	$COCH_3$	Cl	*n*			226–227	$C_{17}H_{14}ClN_3O_2$	327.8	C, H, N, Cl	129	>2630	36	>2630
1u	C_6H_5	H	$COCH_3$	CF_3	*n*			185–187	$C_{18}H_{14}F_3N_3O_2$	361.3	C, H, N, F	25	400	58	>1083
1v	C_6H_5	H	$COOC_2H_5$	Cl	*n*			187–189	$C_{18}H_{16}ClN_3O_3$	357.8	C, H, N, Cl	290	>3220	68	>3220
8	Chlordiazepoxide											26	540	61	2000

[a]Albino mice (NMRI) of 20–25-g weight were used and also albino rats (FW 49) of 140–200-g weight. The test substances were suspended in olive oil and administered intragastrically by way of an esophageal cannula. The dose in mg/kg being effective in 50% of the animals is stated (ED_{50}, LD_{50}). These values were obtained graphically from dose-action curves. In all experiments ten animals were used for each dose and the untreated groups. No statistical analysis of the data was employed. [b]Occurrence of ataxia during 8 hr following the application of the drug. [c]Animals lying on their sides, being unable to stand on their feet. The spinal righting reflex still maintains. [d]Electroshock applied by eye electrodes (90 V, 30 mA, 50 Hz sinusoidal, 0.5 sec), prevention of maximum extension seizure: J. E. Toman, E. A. Swinyard, L. S. Goodmann, M. Merkin, and M. Morata, *J. Neurophysiol.*, **9**, 231 (1946). [e]Determination of the lethality within an observation period of 24 hr. [f]N: calcd, 14.74; found, 14.23. [g]Br: calcd, 24.18; found, 23.63. [h]C: calcd, 66.90; found, 65.67. [i]H: calcd, 4.55; found, 5.03. [j]N: calcd, 16.47; found, 16.02. [k]From benzodiazepines **3**: A, *via* imino chloride **10**; B, *via* imino-ether **11**; C, *via* imino sulfide **12**. [l]Methanesulfonate. [m]**1s** was of chemical interest only and not tested pharmacologically. [n]See Experimental Section.

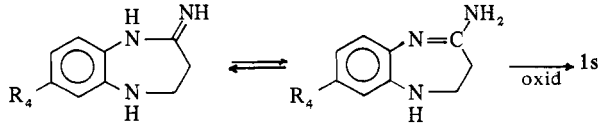
dation[13] from the corresponding substituted tetrahydrobenzodiazepinone of type **5**. In connection with their biochemical properties, these compounds will be dealt with more thoroughly. The iminoether **11** was obtained by conversion of **3** with boron trifluoride etherate and the imino sulfide **12** similarly from **3** by alkylation of the 4-thione prepared by selective thionation of the 4-carbonyl group.[14] Otherwise, substituted compounds **1** were obtained also by reaction of *o*-phenylenediamines with β-chlorocarbonyl-α-chloroenamines.[15]

Compounds **1** with R_1 = H cannot be produced through the same procedure as a further enolizable group is present. Therefore, we synthesized one of these compounds by ring closure of the aminonitrile **13a** to **14** which could be oxidized (**1s**) in a similar way as 1,4-benzodiazepines.[16-18] We obtained **13a** by addition of acrylonitrile[19] to 2-amino-4-chloronitrobenzole in pyridine, in the presence of potassium carbazolate[20] and subsequent reduction of the nitro group of **13b** (see Scheme II).

Scheme II



13a, R_4 = Cl; R = NH_2
b, R_4 = Cl; R = NO_2



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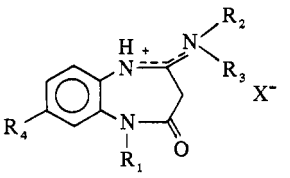
The amidines **1** are quite thermostable and, with lower alkyl groups R_2 and R_3, form water-soluble hydrochlorides and methanesulfonates. The structure of the salts apparently coincides with structure **15**.[21] Compounds **1t-v** were obtained from **1a** and **1b** through acylation with either acetic anhydride or ethyl chloroformate. The nmr spectra showed the expected signals in the aliphatic and aromatic regions; *e.g.*, **1k** (in DMSO-d_6) δ 2.8 (NCH_3), 3.2 (CH_2), 6.8-7.5 ppm (arom H). In solutions of **15** the C-3 protons were interchangeable with the deuterium in D_2O.



15, X = Cl, CH_3SO_3

Pharmacology. Some of the compounds in series **1** inhibit the maximum extensor seizures in mice (Table I). In most compounds this anticonvulsive action is in an order of magnitude similar to that of chlordiazepoxide. The parent substances and the compounds with short side chains are particularly effective. Compared with 1,4-benzodiazepines (*e.g.*, **8**) an interference with motor coordination only occurs at relatively large doses. The high LD_{50} indicates a relatively low toxicity, which applies particularly to the 8-nitro-substituted products (*e.g.*, **1c** and **1n**). Table II shows the activity of some selected benzodiazepines of the type **1** compared with chlordiazepoxide **8** in a series of special tests. In mice some of these compounds exert an anxiolytic action and, with considerably higher doses, inhibit exploratory behavior[22] and the locomotion in an open field;[23] they also demonstrate a marked antagonistic effect against pentylenetetrazole,[24] strychnine, and tremorine.[25] However, the Straub effect due to morphine is not inhibited. Furthermore, some of the compounds **1** cause a taming effect in the mink[26] and possess an anxiolytic action in rats exposed to a conflict in a discriminative passive avoidance situation,[27] both tests being rather specific for minor tranquilizers. The lack of effect in the active avoidance test[28] indicates the absence of major tranquilizer properties.

Table II. Pharmacological Profile of Some Compounds of Type **1**

Species	Test[a]	1b	1c	1j	1n	1u	1v	8
Mouse	Inhibition[b] of motor coordination (ED_{50})	163	30	>103	16	26	70	15
Mouse	Anxiolysis[c] (DE_{50})	3	17	>310	>324	160	39	7
Mouse	Inhibition[d] of exploration (DE_{50})	200	180	310	135	100	>356	130
Mouse	Inhibition[e] of locomotion (DE_{50})	>1000	750	210	170	>360	290	180
Mink	Taming[f] effect (ED_{50})	80	20	>100	80	50	50	10
Rat	Inhibition of active avoidance[g] (DE_{50})		>135		>135			>40
Rat	Inhibition of passive avoidance[h] (DT_{10})	32	26	>135	96	>135	>135	10.5
Rat	Prevention of max electric shock[i] (ED_{50})	16	140	>103	17	92	>119	37
Mouse	Pentylenetetrazole antagonism[j] (ED_{50})	7	8	>90	6	24	30	3.8
Mouse	Strychnine antagonism[k] (ED_{50})	>100	100		19	33		32
Mouse	Tremorine antagonism[l] (ED_{50})	22	1	>80	1	11	>20	2
Mouse	Morphine antagonism[m] (ED_{50})	>90	>100	>90	>100	>90	>90	25

[a] Albino mice (NMRI) of 20-25-g body weight, albino rats (FW 49) of 140-200-g body weight, and minks from a fur-animal farm were used. The test substances usually were suspended in olive oil; in *f* a 1% solution of hydroxyethylmethylcellulose was used. In all cases intragastric administration was carried out using an esophageal cannula. The effective dose is given in mg/kg. No statistical analysis of the data was employed. [b] Dose at which 50% of the animals slide down on an inclined plane: O. Nieschulz and K. Popendicker, *Arzneim.-Forsch.*, **5**, 458 (1955). [c] Dose at which the locomotion in an open field[23] is increased to 50% indicating an anxiolytic effect. [d] Dose causing a 50% decrease of exploration in the Planche à Trous situation.[22] [e] Dose causing a 50% attenuation of locomotion in the open-field test.[23] [f] Dose eliciting an inhibition of aggressiveness or an occurrence of a taming effect in 50% of the animals.[26] [g] Dose at which the conditioned bar-pressing response necessary to avoid an electroshock punishment is reduced to 50%.[28] [h] Dose at which the animals being in a conflict situation made ten lever presses in order to receive food even though a simultaneous signal indicates the association of the reward with an electric shock punishment.[27] [i] Electroshock applied by eye electrodes (90 V, 30 mA, 50 Hz sinusoidal, 1.0 sec); dose at which the maximum extensor seizure is prevented in 50% of the animals: E. A. Swinyard, W. C. Brown, and L. S. Goodmann, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952). [j] Dose at which the lethal effect of 125 mg/kg of pentylenetetrazole administered intraperitoneally 1 hr after the test substance is prevented in 50% of the animals.[24] [k] Dose at which the lethal effect of 1.9 mg/kg of strychnine sulfate injected intraperitoneally 1 hr after dosing with the test substance is prevented in 50% of the animals. [l] Dose causing a 50% inhibition of the tremor due to subcutaneous injection of 40 mg/kg of tremtremorine,[25] the degree of tremor being ascertained subjectively and given arbitrary scores. [m] Dose preventing in 50% of the animals the Straub phenomena due to 30 mg/kg of morphine sulfate injected intraperitoneally.

Discussion

The compounds **1** obviously have similar pharmacological properties as the chemically related **8**. Thus, the assumed pharmacologic analogy has been confirmed. Within the amidine series **1** and also in comparison to **8** differences in their profiles of action have been found. Most effective were the parent substances ($R_2 = R_3 = H$) and those derivatives with short alkyl or acyl chains. Compounds **1** with longer C chains showed a markedly lower effect. Contrary to the benzodiazepinediones **3**, substitution with electronegative substituents in the ortho position of the phenyl group R_1 caused no increase in effect. To a certain extent the compounds with $R_4 = Cl$ and CF_3 were more effective than those with $R_4 = NO_2$ but usually also more toxic. The rate of effectiveness to toxicity was most favorable for the 8-nitro parent substances with short alkyl or acyl chains.

Experimental Section

The melting points are uncorrected and the yields are not optimized. Ir and nmr spectra were consistent with assigned structures.

4-Amino-1-aryl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (1a–r) from 3 *via* the Imino Chloride 10. General Procedure (Method A). PCl_5 (50 g, 0.24 mol) was added to a solution of 0.03 mol of 1*H*-1,5-benzodiazepine-2,4-(3*H*,5*H*)-dione (**3**) in 750 ml of absolute dioxane and stirred during the process. After reaction for 60 min the suspension was ice cooled and stirred with excess amine. The use of liquid ammonia makes cooling unnecessary; a rapid stream of gaseous amine can also be introduced until the suspension gives an alkaline reaction. The mixture was stirred for another 30 min. Then it was evaporated *in vacuo* and the residue stirred with cold aqueous NH_3. This was shaken with CH_2Cl_2, washed with H_2O, dried with $MgSO_4$, and again evaporated. The residue was recrystallized from MeOH, CH_2Cl_2, EtOAc, $(i\text{-Pr})_2O$, or mixtures thereof. In preparations of **1** in which $R_2 = R_3 = H$ it is practicable to take up the residue in absolute Me_2CO and to separate the product from unaltered starting material by precipitation with Et_2O–HCl. The base can then be released with aqueous NH_3 and recrystallized.

1 from Ether 11 or Thioether 12 (Methods B and C, respectively). Either 0.02 mol of 4-ethoxy-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (**11**) or 4-methylmercapto-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (**12**) was suspended or dissolved (according to solubility) in 60 ml of EtOH and 5 ml of DMSO. Excess amine was then added and heating was carried out for 2–3 hr. An autoclave was used with gaseous amines or they were led into the solution boiling under reflux. After cooling and evaporation *in vacuo* the residue was extracted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, and again evaporated. The residue was recrystallized (according to solubility) from EtOH, EtOAc, $(i\text{-Pr})_2O$, or their mixtures.

3-(5-Chloro-2-nitrophenylamino)propionitrile (13b). Acrylonitrile (11 g, 0.205 mol) was poured quickly into a mixture of 30 g (0.174 mol) of 5-chloro-2-nitroaniline, 30 ml of pyridine, and 0.6 g of potassium carbazolate while being stirred. After heating at 70° for 30 min $(i\text{-Pr})_2O$ was added, and the precipitate was filtered by suction and washed with $(i\text{-Pr})_2O$: yield, 29.5 g (75.4%); mp 152–154°.

3-(5-Chloro-*o*-phenylenediamino)propionitrile (13a). **13b** (10 g, 0.0445 mol) was dissolved in MeOH and reduced with Raney nickel–H_2 at room temperature and 5 atm of pressure. After completion of hydrogen uptake it was passed over kieselguhr and evaporated *in vacuo* and the residue was recrystallized from a little CH_2Cl_2–Et_2O: yield, 5.46 g (63%); mp 87–89°.

4-Amino-8-chloro-1*H*-2,3-dihydro-1,5-benzodiazepine (14). Saturated ethereal HCl was mixed with a solution of 2 g (0.0102 mol) of **13a** in 10 ml of absolute THF. Dry HCl gas was then passed through for 2 hr and the composition was allowed to stand for 15 hr at room temperature. Absolute Et_2O was then added carefully and the precipitate filtered by suction and dissolved in H_2O. This was then made alkaline with 6 *N* NaOH and repeatedly shaken with CH_2Cl_2. The CH_2Cl_2 phase was washed with H_2O, dried with $MgSO_4$, and filtered by suction over kieselguhr. After evaporating *in vacuo* the residue was recrystallized from a little CH_2Cl_2–$(i\text{-Pr})_2O$: yield, 1.3 g (65%); mp 143–144°. *Anal.* ($C_9H_{10}ClN_3$, mol wt 195.7) C, H, N, Cl.

4-Amino-8-chloro-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (1s). **14** (5 g, 0.0264 mol) was dissolved in 500 ml of Me_2CO and in small portions mixed with 25 ml of chromic acid (2.67 g of CrO_3 and 2.3 ml of concentrated H_2SO_4 diluted with H_2O to 10 ml). The mixture was stirred at room temperature for 5 hr. It was then poured into ice–water, neutralized with 2 *N* NaOH, shaken with CH_2Cl_2, dried with $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from Me_2CO and dried over P_2O_5, yield 1.7 g (31.7%).

4-Acetylamino-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (1t,u). Either **1a** or **1b** (0.01 mol) was heated under reflux with 7 ml of Ac_2O in 150 ml of absolute C_6H_6. After evaporation *in vacuo* the residue was stirred with water and repeatedly extracted with CH_2Cl_2. After drying with $MgSO_4$ the solvent was evaporated and the residue recrystallized from $(i\text{-Pr})_2O$. The yields were 85 and 91%.

4-Ethoxycarbonylamino-8-chloro-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (1v). **1a** (0.01 mol) was dissolved in 150 ml of absolute C_6H_6 and 10 ml of pyridine and mixed with 0.012 mol of ethyl chloroformate. It was allowed to react under ice cooling for 30 min and then stirred into ice–water. After neutralization with 2 *N* HCl, it was extracted with EtOAc. Finally the solvent was dried with $MgSO_4$ and evaporated *in vacuo*, and the residue was crystallized from EtOAc–$(i\text{-Pr})_2O$, yield 68%. Melting points and analytical data of the compounds **1s–v** are given in Table I.

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