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5-Aryl-1,5-dihydro-2*H*-1,4-benzodiazepin-2-one Derivatives as Antianxiety Agents

Masaru Ogata,* Hiroshi Matsumoto, and Katsumi Hirose

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan. *Received December 16, 1976*

A new series of 7-chloro- and 7-nitro-5-methoxy-5-phenyl-1,5-dihydro-2*H*-1,4-benzodiazepin-2-ones (**7a**,**c**–**e**) was synthesized and found to have potent antipentylenetetrazole activity. These compounds were also employed as intermediates in the synthesis of 3-substituted 1,3-dihydro-1,4-benzodiazepin-2-ones (**8f**–**v**).

A vast number of 1,4-benzodiazepines have been synthesized by a variety of methods and extensive data on their pharmacological activity have been accumulated. Most of the marketed 5-aryl-1,4-benzodiazepines have a double bond at C-4,5 (1,3-dihydro type) and not a C-3,4 (1,5-dihydro type). In connection with this structural problem, Bell et al.[1] showed that 7-chloro-1,5-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1**)[1,2] is less potent than its isomer 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**2a**). These observations prompted us to extend the synthetic research to other 1,5-dihydro-1,4-benzodiazepines which might have potent actions on the central nervous systems and led to the discovery that 1,5-dihydro-5-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (**7a**,**c**–**e**) are potent agents.

Chemistry. The addition reaction of acetyl nitrate has been frequently employed on the olefinic bond.[3] We examined the addition reaction of acetyl nitrate to the C=N bond in 1,4-benzodiazepines **2a**–**e**. Reaction of 7-chloro-1,4-benzodiazepine (**2a**) with fuming nitric acid (d = 1.50) in acetic anhydride at ca. 40 °C resulted in the recovery of starting material as its nitric acid salt. However, when **2a** was converted into the known 1-chloro-1,4-benzodiazepine (**2b**),[4] before subjecting conditions similar to those for **2a**, an insoluble adduct (**3b**) was obtained in 76% overall yield. That the addition reaction had occurred was indicated by the IR spectrum which showed a strong acetoxy carbonyl band at 1723 cm^{-1}. Compound **3b** is unstable when heated in aqueous dioxane leading to formation of the benzophenone derivative **4a** which cyclized to the carbostyril derivative **5a** with aqueous potassium carbonate.

When **3b** was treated with an equimolar amount of methylamine in dichloromethane at room temperature, the dechlorinated product **3a** was obtained in 94% yield. Refluxing **3a** with methanol afforded the methoxy compound **6a** (81%), which was allowed to stand in dichloromethane in the presence of triethylamine at room temperature, giving 1,5-dihydro-1,4-benzodiazepine (**7a**) in 68% yield (see Scheme I).

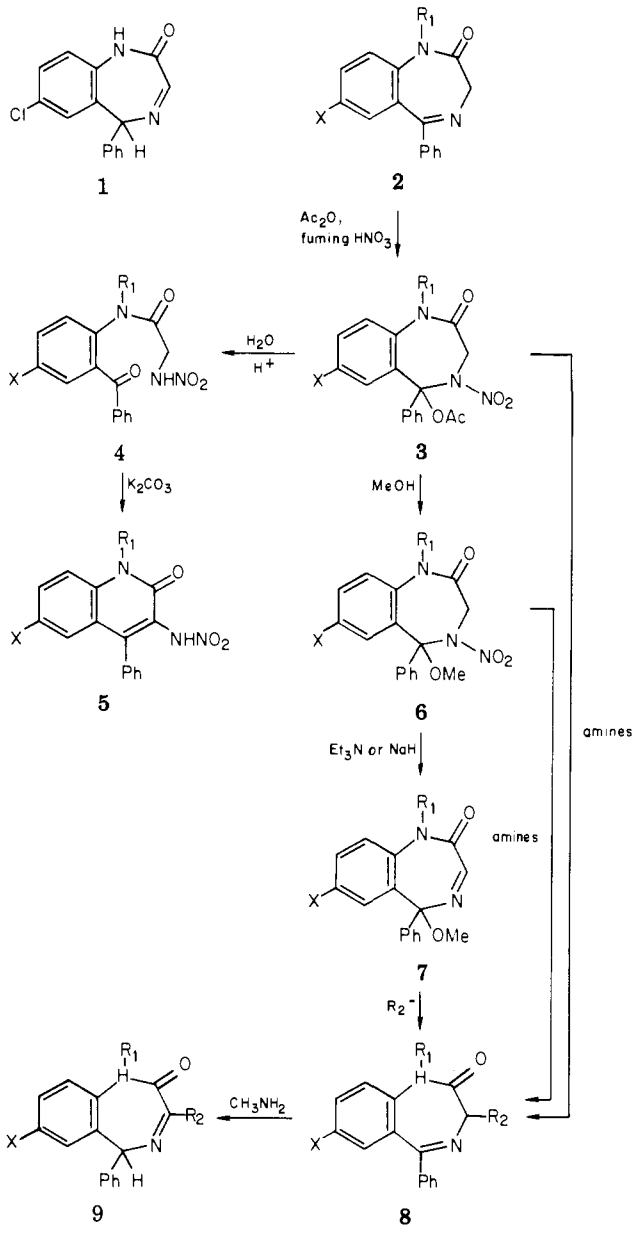
We also studied the reaction of 7-nitro-1,4-benzodiazepine (**2c**) with acetyl nitrate under similar conditions. Treatment of **2c** afforded the insoluble adduct **3c** in 75% yield, without precipitation of the nitric acid salt of the starting material. When **3c** was heated under reflux with aqueous acetic acid, the benzophenone derivative **4c** was obtained, analogous to the reaction of **4a**. To obtain 1,5-dihydro-1,4-benzodiazepine (**7c**), methanolysis was applied to **3c** to give the methoxy compound **6c** (88%), which was treated with triethylamine at room temperature to give 1,5-dihydro-1,4-benzodiazepine (**7c**) in 92% yield.

This reaction could be used to prepare other 5-methoxy-1,5-dihydro-1,4-benzodiazepines as shown by the synthesis of the 1-methyl analogues **7d**,**e**. Namely, the 1,5-dihydro-1,4-benzodiazepines **6d** and **6e** were prepared from **2d** and **2e** in satisfactory yield via addition of acetyl nitrate followed by methanolysis of the resulting adduct (**3d** and **3e**, respectively). Elimination of nitrous acid from **6d** with triethylamine was markedly slow under similar conditions as for **6a** and resulted in formation of 5-methoxy-1,5-dihydro-1,4-benzodiazepine (**7d**) contaminated with the starting material (**6d**). Treatment of **6e** with triethylamine gave not the analogous 1,5-dihydro-1,4-benzodiazepine (**7e**) but the starting material, although a long reaction time was allowed.

Treatment of **6d** with sodium hydride in dimethylformamide at −30 °C resulted in a 44% yield of **7d**. N-Methylation of **7a** and **7c** as another synthetic route to **7d** and **7e** was tried. Treatment of **7a** and **7c** with methyl iodide in the presence of sodium hydride in dimethylformamide at low temperature afforded **7d** and **7e** in 61 and 74% yield, respectively.

We found that the 1,5-dihydro-1,4-benzodiazepines **7a**,**c**–**e** could be used as intermediates in the synthesis of 3-substituted 1,3-dihydro-1,4-benzodiazepines **8f**–**v**. When **7a** was allowed to stand at room temperature in aqueous dioxane containing a trace amount of hydrochloric acid or *p*-toluenesulfonic acid, the known 3-hydroxy-1,3-dihydro-1,4-benzodiazepine (**8f**, oxazepam)[5] was obtained in 66% yield. By analogy, **7c**, **7d**, and **7e** underwent hydroxylation to form the corresponding 3-hydroxy-1,3-dihydrobenzodiazepines (**8g**,[6] **8h**,[5] and **8i**[6]) as shown in Table I. An analogous nucleophilic reaction of **7a** and **7e** at the 3 position proceeded easily upon treatment with methanol, ethylene glycol, ethylene chlorohydrin, hydroxylamine, sodium cyanide, and methylamine to give the corre-

Scheme I



	R_1	R_2	X		R_1	R_2	X
a	H		Cl	l	H	$O(CH_2)_2OH$	NO_2
b	Cl		Cl	m	H	$O(CH_2)_2Cl$	Cl
c	H		NO_2	n	H	$O(CH_2)_2Cl$	NO_2
d	CH_3		Cl	o	H	OMe	NO_2
e	CH_3		NO_2	p	H	NHOH	Cl
f	H	OH	Cl	q	H	CN	Cl
g	H	OH	NO_2	r	H	CN	NO_2
h	CH_3	OH	Cl	s	H	$NHCH_3$	Cl
i	CH_3	OH	NO_2	t	CH_3	$NHCH_3$	NO_2
j	H	OMe	Cl	u	H	NH_2	Cl
k	H	$O(CH_2)_2OH$	Cl	v	H	NC_5H_{10}	NO_2

sponding 3-substituted 1,3-dihydro-1,4-benzodiazepines **8j–t** as shown in Table I.

To prepare the 3-substituted amino-1,3-dihydro-1,4-diazepines **8s–v**, the corresponding 5-acetoxy-1,4-benzodiazepine (**3a**) or 5-methoxy-1,4-benzodiazepines (**6a,c**) could be employed as well as the above-mentioned 1,5-dihydro-1,4-benzodiazepines (**7a,e**). Treatment of **3a** and **6a** with methylamine in dichloromethane at room temperature yielded the 3-methylamino-1,3-dihydro-1,4-benzodiazepine (**8s**, 11 and 99%, respectively), and also **6a** could be converted to the 3-amino-1,3-dihydro-1,4-benzodiazepine (**8u**,[8] 83%) under similar conditions. When piperidine was used, **6c** gave the 3-piperidino-1,3-dihydro-1,4-benzodiazepine (**8v**, 57%). These results provide a relatively simple route to a variety of 3-substituted 1,3-dihydro-1,4-benzodiazepines.[9] Details are given in the Experimental Section.

Table I. 3-Substituted 1,3-Dihydro-1,4-benzodiazepin-2-ones

Starting material	Nucleophile	Product	Yield, %
7a	H_2O (dioxane, HCl)	**8f** (oxazepam)[a]	66
7c	H_2O (THF, HCl)	**8g**[b]	68
7d	H_2O (THF, HCl)	**8h**[a]	29
7e	H_2O (THF, HCl)	**8i**[b]	56
7a	MeOH (*p*-TsOH)	**8j**[c]	87
7a	$HOCH_2CH_2OH$ (HCl)	**8k**	80
7e	$HOCH_2CH_2OH$ (HCl)	**8l**	52
7a	$ClCH_2CH_2OH$ (HCl)	**8m**	35
		8j	32
7e	$ClCH_2CH_2OH$ (HCl)	**8m**	45
		8o	21
7a	NH_2OH (H_2O)	**8p**	70
7a	NaCN (H_2O)	**8q**	83
7e	NaCN (H_2O)	**8r**	42
7a	CH_3NH_2 (CH_2Cl_2)	**8s**	67
7e	CH_3NH_2 (CH_2Cl_2)	**8t**	56

[a] Reference 5. [b] Reference 6. [c] Reference 7.

Several 3-substituted 1,3-dihydro-1,4-benzodiazepines (**8j,s,t**) rearranged to the isomeric 1,5-dihydro-1,4-benzodiazepines (**9j,s,t**) upon treatment of dimethylamine in dioxane at room temperature although the reaction time was long (60–70 h), as shown in the Experimental Section. Similar rearrangement of 3-substituted 5-aryl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones has been observed by other workers[10] (see Table II).

Pharmacology. Acute toxicity was determined in mice. Oral LD_{50} values were calculated by the Bliss method.[11]

A rotarod performance test[12] was used to estimate muscle relaxant activity. The test used as a measure of tranquilizing activity was antagonism of pentylenetetrazole-induced convulsions in mice.[13] Maximal electroshock test[14] was used as a measure of anticonvulsant activity. ED_{50} values were calculated by the Bliss method.[11]

Table II gives the results along with the data for diazepam (**2d**). All the 5-methoxy-1,5-dihydro-1,4-benzodiazepines (**7a,c–e**) were active, especially **7d** and **7e** which were more potent than diazepam (**2d**).

As shown in the Experimental Section, considerable susceptibility of the 5-methoxy-1,5-dihydro-1,4-benzodiazepines (**7a,c–e**) to aqueous acid was indicated by the formation of 3-hydroxy-1,3-dihydro-1,4-benzodiazepines (**8f–i**). Conversion of 5-methoxy-1,5-dihydro-1,4-benzodiazepines (**7a,c–e**) in vivo into 3-hydroxy-1,3-dihydro-1,4-benzodiazepines (**8f–i**) seems very likely. Comparing the data for unmethylated and 1-methylated pairs, e.g., 3-hydroxy-1,3-dihydro-1,4-benzodiazepines (**8f** and **8h**)[7] shows that no little difference arises in the pentylenetetrazole test by methylation; such a relationship holds for 3-hydroxy-7-nitro-1,3-dihydro-1,4-benzodiazepines (**8g** and **8i**).[15] However, 5-methoxy-1,5-dihydro-1,4-benzodiazepine (**7d**) has twice the potency of its unmethylated analogue **7a**, and such a relationship holds for the 7-nitro compounds **7c** and **7e**. Differences in observed oral activities can reflect, among other factors, the differences in dissolution rates in the gut, rates of hydrolyses before and after absorption, and rates of metabolism.

Experimental Section

Melting points were determined on a Yanagimoto micromelting

Table II. Pharmacological Data

Compd	Acute toxicity, LD_{50}, mg/kg, oral	Muscle relaxant act. (mice), ED_{50}, mg/kg, oral; rotarod performance test	Anticonvulsant act. (mice), ED_{50}, mg/kg, oral	
			Antimax shock	Antipentylene-tetrazole
2d (diazepam)	>1000	14.4	62.2	1.2
3c	>1000	>100	>100	58.0
6a	>1000	>100	>100	>100
6c	>1000	>100	>100	13.0
6d	>1000	>100	>100	>100
7a	>1000	28.1	>100	1.6
7c	>1000	19.1	>100	1.4
7d	>1000	27.5	53.0[b]	0.7[b]
7e	750	5.2[a]	76.0	0.7[b]
8k	>1000	>100	>100	36.0
8l	>1000	>100	>100	9.2
8m	>1000	>100	>100	13.0
8n	>1000	>100	>100	9.2
8p	>1000	>100	>100	32.0
8q	>1000	>100	>100	14.0
8r	>1000	>100	>100	>100
8u	>1000	>100	>100	85.0
9t	>1000	>100	>100	>100

[a] Significant difference vs. diazepam ($p < 0.05$).[11] [b] Not significant difference vs. diazepam.[11]

apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60 or Varian T-60 instrument with Me_4Si as internal standard. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Silica gel, Merck (70–230 mesh), was used for chromatography. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

5-Acetoxy-1,7-dichloro-4-nitro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (3b). To a solution of 1.1 g (4.1 mmol) of **2a** in 16 mL of CH_2Cl_2, 8 mL (16 mmol) of 13.5% NaOCl was added dropwise at room temperature. After the mixture had been stirred for 15 min, H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated at room temperature. To a solution of the resulting residue (**2b**) in Ac_2O (10 mL), fuming HNO_3 (d = 1.50, 1.1 mL) was added with stirring at ca. 40 °C. After 5 min, the resulting precipitate was filtered and washed with Et_2O to give 1.26 g (76%) of **3b**: mp 132 °C dec; IR (Nujol) 1750, 1718 cm^{-1}. Anal. ($C_{17}H_{13}Cl_2N_3O_5$) C, H, Cl, N.

5-Chloro-2-nitroacetamidobenzophenone (4a). A solution of 200 mg of **3b** in 5 mL of dioxane and 1 mL of H_2O was heated for 30 min at 100 °C. After removal of the solvent in vacuo, the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was washed with isopropyl ether to give 124 mg (46%) of **4a**, mp 134–138 °C. Recrystallization from a mixture of benzene and isopropyl ether gave the pure sample: 81 mg (31%); mp 137–138 °C; IR (Nujol) 3220, 1701, 1680, 1639, 1620, 1571 cm^{-1}. Anal. ($C_{15}H_{12}ClN_3O_4$) C, H, Cl, N.

6-Chloro-3-nitroamino-4-phenyl-2(1*H*)-quinolone (5a). A mixture of 300 mg of **4a**, 7.5 mL of 5% aqueous K_2CO_3, and 7.5 mL of MeOH was heated at 70 °C for 20 min. The reaction mixture was cooled and made acidic with dilute HCl. The resulting solid was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was washed with isopropyl ether to give 220 mg of **5a**. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: 164 mg (58%); mp 172–173 °C dec; IR (Nujol) 3240, 1670, 1570 cm^{-1}. Anal. ($C_{15}H_{10}ClN_3O_3$) C, H, Cl, N.

5-Acetoxy-7-chloro-4-nitro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (3a). To a solution of 1.37 g (3.3 mmol) of **3b** in 13.7 mL of CH_2Cl_2, 1.33 g (3.3 mmol) of 7.8% CH_3NH_2–CH_2Cl_2 was added at room temperature. After the mixture was stirred for 1 h, H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated. The residual oil was crystallized from a mixture of CH_2Cl_2 and isopropyl ether to give 1.18 g (94%) of **3a**, mp 128–130 °C dec. Repeated recrystallization from a mixture of AcOEt and Et_2O gave **3a** (606 mg, 48%): mp 138–142 °C dec; IR (Nujol) 3275, 1723, 1705, 1695 cm^{-1}; NMR (Me_2SO-d_6) 2.42 (s, 3 H, OAc), 4.95 (d, 1 H) and 5.15 (d, 1 H) (AB system, J = 15.0 Hz, C_3-H), 7.00–7.93 (m, 8 H, aromatic H), 10.50 (br, 1 H, CONH). Anal. ($C_{17}H_{14}ClN_3O_5$) C, H, Cl, N.

7-Chloro-5-methoxy-4-nitro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (6a). A mixture of **3a** (1.17 g) and MeOH (35 mL) was heated under reflux for 25 min and evaporated. The resulting crystals were filtered and washed with a mixture of Et_2O and isopropyl ether to give 872 mg (81%) of **6a**: mp 208–210 °C dec; IR (Nujol) 3200, 1700 cm^{-1}; NMR (Me_2SO-d_6) 3.47 (s, 3 H, OMe), 4.70 (d, 1 H) and 5.25 (d, 1 H) (AB system, J = 15.0 Hz, C_3-H), 6.95–7.73 (m, 8 H, aromatic H), 10.43 (br, 1 H, CONH). Anal. ($C_{16}H_{14}ClN_3O_4$) C, H, Cl, N.

7-Chloro-1,5-dihydro-5-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7a). To a solution of 200 mg (0.6 mmol) of **6a** in 20 mL of CH_2Cl_2, 485 mg (4.8 mmol) of Et_3N was added at room temperature. After the mixture was stirred for ca. 3 h, the organic layer was washed with H_2O and dried over Na_2SO_4, filtered, and evaporated. The residue was filtered and washed with isopropyl ether to give 117 mg (68%) of **7a**, mp 181–186 °C. Recrystallization from isopropyl ether gave **7a** (64 mg, 37%): mp 188 °C; IR (Nujol) 3190, 1085, 1641 cm^{-1}; NMR ($CDCl_3$) 3.25 (s, 3 H, OMe), 6.83–7.50 (m, 8 H, aromatic H), 7.97 (s, 1 H, C_3-H), 11.13 (br, 1 H, CONH). Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, Cl, N.

5-Acetoxy-4,7-dinitro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (3c). To a suspension of **2c** (500 mg) and Ac_2O (8 mL), 0.5 mL of fuming nitric acid (d = 1.50) was added with stirring at ca. 40 °C. After the mixture had been stirred for 30 min, the resulting precipitate was filtered and washed with Et_2O to give 515 mg (75%) of **3c**, mp 169–170 °C dec. Recrystallization from a mixture of CH_2Cl_2 and AcOEt gave the pure sample: mp 174–175 °C dec; IR (Nujol) 3160, 1768, 1720 cm^{-1}; NMR (Me_2SO-d_6) 2.45 (s, 3 H, OAc), 5.00 (d, 1 H) and 5.18 (d, 1 H) (AB system, J = 17.0 Hz, C_3-H), 7.20–7.67 (m, 6 H, aromatic H), 8.05–8.43 (m, 2 H aromatic H), 10.12 (br, 1 H, CONH). Anal. ($C_{17}H_{14}N_4O_7$) C, H, N.

4,7-Dinitro-5-methoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (6c). A solution of **3c** (100 mg) in MeOH (5 mL) was heated under reflux for 1 h and evaporated. The resulting crystals were filtered and washed with a mixture of AcOEt and isopropyl ether to give 82 mg (88%) of **6c**, mp 198–199.5 °C dec. Repeated recrystallization from a mixture of CH_2Cl_2 and MeOH gave the pure sample: mp 208 °C dec; IR (Nujol) 3240, 1728 cm^{-1}. Anal. ($C_{16}H_{14}N_3O_6$) C, H, N.

2-Nitroaminoacetamido-5-nitrobenzophenone (4c). A solution of **3c** (300 mg) in AcOH (6 mL)–H_2O (0.6 mL) was heated on a water bath for 5 min. After the addition of H_2O, the resulting precipitate was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was washed with a mixture of isopropyl ether and AcOEt to give 239

mg (90%) of **4c**, mp 176–177 °C. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: 193 mg (72%); mp 177–177.5 °C dec; IR (Nujol) 3240, 1733, 1620 (shoulder), 1615 cm^{-1}; NMR (Me_2SO-d_6) 4.13 (s, 2 H, CH_2), 7.33–8.67 (m, 8 H, aromatic H), 10.80 (br, 1 H, CONH). Anal. ($C_{15}H_{12}N_4O_6$) C, H, N.

1,5-Dihydro-5-methoxy-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7c). To a solution of 600 mg (1.7 mmol) of **6c** in 30 mL of CH_2Cl_2, 516 mg (5.1 mmol) of Et_3N was added at room temperature. After the mixture was stirred for 10 min, the organic layer was washed with H_2O and dried over Na_2SO_4, filtered, and evaporated. The residue was filtered and washed with Et_2O to give 481 mg (92%) of **7c**: mp 205 °C dec; IR (Nujol) 3200, 1683, 1642 cm^{-1}. Anal. ($C_{16}H_{13}N_3O_4$) C, H, N.

5-Acetoxy-7-chloro-1-methyl-4-nitro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (3d). To a suspension of **2d** (1.0 g) and Ac_2O (10 mL), 1.0 mL of fuming HNO_3 (d = 1.50) was added with stirring at ca. 40 °C. After the mixture had been stirred for 20 min, the resulting precipitate was filtered and washed with Et_2O to give 1.5 g (84%) of **3d**, mp 157 °C dec. Recrystallization from a mixture of AcOEt and CH_2Cl_2 gave the pure sample: mp 158–159 °C dec; IR (Nujol) 1764, 1699, 1543 cm^{-1}. Anal. ($C_{18}H_{16}ClN_3O_5$) C, H, Cl, N.

7-Chloro-5-methoxy-1-methyl-4-nitro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (6d). A solution of **3c** (200 mg) and MeOH (10 mL) was heated under reflux for 1 h and evaporated. The resulting crystals were filtered and washed with a mixture of AcOEt and isopropyl ether to give 124 mg (67%) of **6d**, mp 197–197.5 °C dec. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: mp 198–198.5 °C dec; 98 mg (53%); IR (Nujol) 1685, 1550 cm^{-1}; NMR ($CDCl_3$) 3.13 (s, 3 H, NMe), 3.50 (s, 3 H, OMe), 4.30 (d, 1 H) and 5.60 (d, 1 H) (AB system, J = 15.0 Hz, C_3H), 6.90–7.97 (m, 8 H, aromatic H). Anal. ($C_{17}H_{16}ClN_3O_4$) C, H, Cl, N.

4,7-Dinitro-1-methyl-5-methoxy-1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6e). To a suspension of **2e** (500 mg) and Ac_2O (5 mL), 0.5 mL of fuming nitric acid (d = 1.50) was added with stirring at ca. 40 °C. After the mixture had been stirred for 15 min, the resulting precipitate was filtered and washed with Et_2O to give 520 mg (77%) of **3e**: mp 146–147 °C dec; IR (Nujol) 1760, 1693, 1550 cm^{-1}.

A solution of the above product (**3e**, 520 mg) in MeOH (21 mL) was heated under reflux for 35 min and cooled. The resulting crystals were filtered to give 285 mg (59%) of **6e**, mp 205–206 °C dec. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: 254 mg (53%); mp 202–204 °C dec; IR (Nujol) 1700, 1542 cm^{-1}; NMR ($CDCl_3$) 3.25 (s, 3 H, NMe), 3.58 (s, 3 H, OMe), 4.32 (d, 1 H) and 5.67 (d, 1 H) (AB system, J = 16.0 Hz, C_3-H), 7.17–7.50 (m, 6 H, aromatic H), 8.00–8.87 (m, 2 H, aromatic H). Anal. ($C_{17}H_{16}N_4O_6$) C, H, N.

7-Chloro-1,5-dihydro-5-methoxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7d). A. A solution of 600 mg (2.0 mmol) of **7a** in 2 mL of dry DMF was cooled to 0 °C and treated with 106 mg (2.2 mmol) of 50% NaH in mineral oil. After the mixture had been stirred for 10 min, MeI (740 mg) (5.2 mmol) was added and stirred at 0 °C for 5 min. The reaction mixture was poured into water and extracted with Et_2O. The Et_2O extracts were washed with water, dried over Na_2SO_4, filtered, and evaporated. The residue was crystallized from isopropyl ether to give 381 mg (61%) of **7d**: mp 146.5–147 °C; IR (Nujol) 1664, 1638, 1630 cm^{-1}; NMR ($CDCl_3$) 2.83 (s, 3 H, NMe), 3.30 (s, 3 H, OMe), 6.77–7.58 (m, 8 H, aromatic H), 7.80 (s, 1 H, C_3-H). Anal. ($C_{17}H_{15}ClN_2O_2$) C, H, Cl, N.

B. To a solution of 200 mg (4.2 mmol) of 50% NaH (in mineral oil) in 7.5 mL of DMF, 500 mg (1.4 mmol) of **6d** was added with stirring at −30 °C. The reaction mixture was stirred at −10 °C for 30 min, poured into ice–water, and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was crystallized from isopropyl ether to give 192 mg (44%) of **7d**, mp 145.5–146.5 °C. This was identified with **7d** derived from **7a** by comparison of their IR spectra.

1,5-Dihydro-5-methoxy-1-methyl-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7e). A. A solution of 920 mg (3.0 mmol) of **7c** in 8 mL of dry DMF was cooled to −30 °C and treated with 156 mg (3.3 mmol) of 50% NaH in mineral oil. After the mixture had been stirred for 15 min, MeI (842 mg) (6.0 mmol) was added and stirred at −30 °C for 10 min. The reaction mixture was poured into H_2O and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was crystallized from a mixture of CH_2Cl_2 and isopropyl ether to give 708 mg (74%) of **7e**, mp 158–160 °C. Repeated recrystallization gave the pure sample: mp 163–164 °C; IR (Nujol) 1667, 1640, 1610 cm^{-1}; NMR ($CDCl_3$) 2.90 (s, 3 H, NMe), 3.28 (s, 3 H, OMe), 6.83–7.67 (m, 7 H, aromatic H), 7.90 (s, 1 H, C_3-H), 9.92 (q, 1 H, J = 9.0, 2.5 Hz, aromatic C_8-H), 10.57 (br, 1 H, CONH). Anal. ($C_{17}H_{15}N_3O_4$) C, H, N.

B. To a solution of 400 mg (1.1 mmol) of **6e** in 10 mL of CH_2Cl_2, 1.1 g (11 mmol) of Et_3N was added at room temperature. After the mixture was stirred for 72 h, the organic layer was washed with H_2O and dried over Na_2SO_4, filtered, and evaporated. The residue was filtered and washed with Et_2O to give 196 mg (a mixture of **7e** and starting material, **6e**, in the ratio of 95:5 by NMR spectra).

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8f). To a solution of **7a** (48 mg) in 2 mL of THF and 1 mL of H_2O, 1 drop of 6 N HCl was added with stirring at room temperature. The reaction mixture was stirred for 1 min at room temperature; excess H_2O was added and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was washed with isopropyl ether to give 37 mg (81%) of **8f**, mp 198–199 °C. Recrystallization from EtOH gave the pure sample: 30 mg (66%); mp 205–207 °C. This was identified with an authentic sample prepared according to the method of Bell et al.[5] by comparison of their IR spectra.

1,3-Dihydro-3-hydroxy-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8g). To a solution of **7c** (135 mg) in 5 mL of THF, 1 drop of 6 N HCl was added with stirring at room temperature. The reaction mixture was stirred at room temperature for 5 min as above. Analogous work-up gave a residue, which was washed with Et_2O to give 96 mg (68%) of **8g**,[6] mp 211 °C dec.

7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8h). To a solution of **7d** (50 mg) in 2 mL of THF and 1 mL of H_2O, 1 drop of 6 N HCl was added with stirring at room temperature. Analogous work-up gave a residue, which was washed with isopropyl ether to give 14 mg (29%) of **8h**, mp 138–139 °C. Recrystallization from cyclohexane gave the pure sample: mp 118.5–119.5 °C (lit.[5] 119–121 °C); 7 mg (15%).

1,3-Dihydro-3-hydroxy-1-methyl-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8i). To a solution of **7e** (200 mg) in 2 mL of THF and 1 mL of H_2O, 1 drop of 6 N HCl was added with stirring at room temperature Analogous work-up gave a residue. The residue was dissolved in CH_2Cl_2 and chromatographed on silica gel and the column was eluted a mixture of CH_2Cl_2 and MeOH. The residue from the fraction eluted with CH_2Cl_2 containing 5–7% MeOH was recrystallized from a mixture of AcOEt and Et_2O to give 108 mg (56%) of **8i**,[6] mp 155.5–156.5 °C. Anal. ($C_{16}H_{13}N_3O_4$) C, H, N.

7-Chloro-1,3-dihydro-3-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8j). To a solution of **7a** (860 mg) in 17 mL of absolute MeOH, 86 mg of p-toluenesulfonic acid was added at room temperature. After the mixture had been stirred at room temperature for 10 min, the resulting precipitate was filtered and washed with Et_2O to give 686 mg (80%) of **8j**,[7] mp 258–260 °C. The filtrate was evaporated and the residue was washed with a mixture of MeOH and Et_2O to give 66 mg (7%) of **8j**,[7] mp 258–260 °C. Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, Cl, N.

7-Chloro-1,3-dihydro-3-(β-hydroxyethoxy)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8k). To a suspension of **7a** (400 mg) and ethylene glycol (8 mL), 2 drops of concentrated HCl was added with stirring at room temperature. After the mixture had been stirred for 40 min, H_2O was added and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was washed with isopropyl ether to give 353 mg (80%) of **8k**, mp 214–216.5 °C. Recrystallization from a mixture of MeOH and Et_2O gave the pure sample: 299 mg (68%); mp 215–218 °C; IR (Nujol) 3420, 1695 cm^{-1}; NMR (Me_2SO-d_6) 3.57–3.83 (m, 4 H, $-CH_2CH_2-$), 4.58 (br, 1 H, OH), 4.83 (s, 1 H, C_3-H), 7.08–7.83 (m, 8 H, aromatic H), 10.78 (br, 1 H, CONH). Anal. ($C_{17}H_{15}ClN_2O_3$) C, H, Cl, N.

1,3-Dihydro-3-(β-hydroxyethoxy)-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8l). To a suspension of **7c** (200 mg) and ethylene glycol (4 mL), 1 drop of concentrated HCl was added with stirring at room temperature. After the mixture had been stirred for 1 h as above, analogous work-up gave a residue, which was washed with Et_2O to give 113 mg (52%), mp 224–226 °C dec. Recrystallization from MeOH gave the pure sample: 75 mg (34%); mp 222–224 °C dec; IR (Nujol) 3420, 1700 cm^{-1}; NMR (Me_2SO-d_6) 3.92–3.50 (m, 4 H, $-CH_2CH_2-$), 4.60 (br, 1 H, OH), 4.95 (s, 1 H, C_3-H), 7.33–7.83 (m, 6 H, aromatic H), 7.21 (d, 1 H, J = 2.5 Hz, aromatic C_6-H), 8.43 (q, 1 H, J = 9.0, 2.5 Hz, aromatic C_8-H), 11.17 (br, 1 H, CONH). Anal. ($C_{17}H_{15}N_3O_5$) C, H, N.

7-Chloro-1,3-dihydro-3-(β-chloroethoxy)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8m) and 7-Chloro-1,3-dihydro-3-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8j). To a suspension of **7a** (500 mg) and ethylene chlorohydrin (10 mL), 2 drops of concentrated HCl was added with stirring at room temperature. After the mixture had been stirred for 2 h, analogous work-up gave a residue, which was chromatographed on silica gel, and the column was eluted with $CHCl_3$ containing 1% MeOH. The residue of fractions 3 and 4 was collected and washed with a mixture of Et_2O and isopropyl ether to give 200 mg (35%) of 8m: mp 189–191 °C dec; IR (Nujol) 3200, 3120, 1690 cm^{-1}; NMR (Me_2SO-d_6) 4.13–3.75 (m, 4 H, $-CH_2CH_2-$), 4.90 (s, 1 H, C_3H), 7.17–7.83 (m, 8 H, aromatic H), 10.82 (br, 1 H, CONH). Anal. ($C_{17}H_{14}Cl_2N_2O_2$) C, H, Cl, N.

The residue of fractions 6–9 was collected and washed with isopropyl ether to give **8j** (159 mg, 32%). This was identified with **8j** derived from **7a** with MeOH containing HCl by comparison of their IR spectra.

3-(β-Chloroethoxy)-1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8n) and 1,3-Dihydro-3-methoxy-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8o). To a suspension of **7c** (400 mg) and ethylene chlorohydrin (8 mL), 2 drops of concentrated HCl was added. Analogous work-up gave a residue, which was chromatographed on silica gel. The residue of fractions 5–7 (solvent, $CHCl_3$ containing 0.5% MeOH) and fractions 8–10 (solvent, $CHCl_3$ containing 1% MeOH) was collected and washed with AcOEt to give 207 mg (45%, mp 194–195.5 °C dec) of **8n**. Recrystallization from a mixture of AcOEt and Et_2O gave the pure sample: 174 mg (38%); mp 196.5–197.5 °C dec; IR (Nujol) 3230, 3160, 1709 cm^{-1}; NMR ($CDCl_3$) 3.67–4.58 (m, 4 H, $-CH_2CH_2-$), 4.97 (s, 1 H, C_3H), 7.33–7.67 (m, 6 H, aromatic H), 8.12–8.50 (m, 2 H, aromatic H), 10.05 (br, 1 H, CONH). Anal. ($C_{17}H_{14}ClN_3O_4$) C, H, Cl, N.

The residue of fractions 12–14 (solvent, $CHCl_3$ containing 1% MeOH) and fractions 15 and 16 (solvent, $CHCl_3$ containing 3% MeOH) was collected and washed wth Et_2O to give 83 mg (21%) of **8o**: mp 270 °C dec; IR (Nujol) 3250, 1719, 1690 cm^{-1}. Anal. ($C_{16}H_{13}N_3O_4$) C, H, N.

7-Chloro-1,3-dihydro-3-hydroxylamino-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8p). To a solution of aqueous NH_2OH, prepared from 580 mg (8.3 mmol) of NH_2OH–HCl in 3 mL of H_2O and 333 mg (8.3 mmol) of NaOH in 1.5 mL of H_2O, 250 mg (0.8 mmol) of **7a** was added under room temperature and the mixture was stirred at room temperature for 1.5 h. The solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was washed with AcOEt to give 176 mg (70%) of **8p**, mp 175–177 °C dec. Recrystallization from MeOH gave the pure sample: 146 mg (58%); mp 178–180 °C dec; IR (Nujol) 3200, 1686 cm^{-1}; NMR (Me_2SO-d_6) 4.33 (br, 1 H, C_3-H, this signal turned into a sharp singlet by addition of D_2O), 6.27 (br, 1 H, NH or OH), 7.08–7.87 (m, 9 H, aromatic 8 H and NH or OH), 10.78 (br, 1 H, CONH). Anal. ($C_{15}H_{12}ClN_3O_2$) C, H, Cl, N.

7-Chloro-3-cyano-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8q). To a solution of 390 mg (1.3 mmol) of **7a** in 9 mL of THF, 636 mg (13.0 mmol) of NaCN in 9 mL of H_2O was added at room temperature. After the mixture was stirred for 30 min, excess H_2O was added, neutralized with 6 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was washed with Et_2O to give 319 mg (83%) of **8q**, mp 239–240.5 °C dec. Recrystallization from MeOH gave the pure sample: 219 mg (57%); mp 241–244 °C dec; IR (Nujol) 3130, 2260, 1723, 1720 cm^{-1}; NMR (Me_2SO-d_6) 5.38 (s, 1 H, C_3-H), 7.22–7.41 (m, 7 H, aromatic H), 7.73 (q, 1 H, J = 9.0, 2.5 Hz, aromatic C_8-H), 11.17 (br, 1 H, CONH). Anal. ($C_{16}H_{10}ClN_3O$) C, H, Cl, N.

3-Cyano-1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8r). To a solution of 400 mg (1.3 mmol) of **7c** in 8 mL of THF, 630 mg (13 mmol) of NaCN in 6 mL of H_2O was added at room temperature. After the mixture was stirred for 20 min, excess H_2O was added, neutralized with 6 N HCl, and extracted with $CHCl_3$. A undissolved material (**8r**), 165 mg (42%, mp 261 °C dec), was filtered. The $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was washed with a mixture of $CHCl_3$ and Et_2O to give 85 mg (22%) of **8r**: mp 261 °C dec; IR (Nujol) 3160, 2260, 1720 cm^{-1}; NMR (Me_2SO-d_6) 5.47 (s, 1 H, C_3-H), 7.43–7.73 (m, 6 H, aromatic H), 8.05 (d, 1 H, J = 2.5 Hz, aromatic C_6-H), 8.48 (q, 1 H, J = 8.5, 2.5 Hz, aromatic C_8-H), 11.67 (br, 1 H, CONH). Anal. ($C_{16}H_{20}N_4O_3$) C, H, N.

7-Chloro-1,3-dihydro-3-methylamino-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8s). A. A solution of 700 mg (1.86 mmol) of **3a** in 50 mL (12.9 mol) of dioxane containing 8% CH_3NH_2 was stirred for 17 h at room temperature. After removal of solvent in vacuo the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to give a residue which was chromatographed on silica gel. The residue of fractions 8 and 9 (solvent, CH_2Cl_2 containing 5% MeOH) and fraction 10 (solvent, CH_2Cl_2 containing 10% MeOH) was collected and washed with a mixture of AcOEt and Et_2O to give 104 mg of **8s**. Recrystallization from a mixture of MeOH and Et_2O gave the pure sample: 60 mg (11%); mp 196.5–200.5 °C dec; IR (Nujol) 3180, 1692 cm^{-1}; NMR (Me_2SO-d_6) 2.47 (s, 3 H, NMe), 4.07 (s, 1 H, C_3-H), 7.00–7.87 (m, 8 H, aromatic H), 10.53 (br, 1 H, CONH). Anal. ($C_{16}H_{14}ClN_3O$) C, H, Cl, N.

B. To a solution of 200 mg (0.6 mmol) of **6a** in 10 mL of CH_2Cl_2, 1 mL of MeOH and 2.3 g (5.8 mmol) of CH_2Cl_2 containing 7.8% CH_3NH_2 were added, and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. Analogous work-up gave a residue, which was washed with a mixture of Et_2O and isopropyl ether to give 170 mg (99%, mp 196.5–198 °C dec) of **8s**.

C. To a solution of 54 mg (0.2 mmol) of **7a** in 2.7 mL (61 mmol) of CH_2Cl_2, 0.2 mL of MeOH and 310 mg (0.8 mmol) of CH_2Cl_2 containing 7.8% CH_3NH_2 were added, and the mixture was stirred for 1.5 h at room temperature. Analogous work-up gave a residue, which was washed with a mixture of isopropyl ether and Et_2O to give 36 mg (67%, mp 196.5–198 °C dec) of **8s**.

1,3-Dihydro-1-methyl-3-methylamino-7-nitro-2*H*-1,4-benzodiazepin-2-one (8t). To a mixture of 196 mg (0.6 mmol) of **7e** in 5 mL of CH_2Cl_2, 2.1 g (5.3 mmol) of CH_2Cl_2 containing 7.8% CH_3NH_2 was added, and the mixture was stirred for 1.5 h at room temperature. Analogous work-up gave a residue, which was washed with a mixture of AcOEt and Et_2O to give 110 mg (56%, mp 151–155 °C) of **8t**. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: mp 153–157 °C; IR (Nujol) 3340, 1685 cm^{-1}; NMR ($CDCl_3$) 2.33 (br, 1 H, NH), 2.62 (s, 3 H, NMe), 3.52 (s, 3 H, NMe), 4.22 (s, 1 H, C_3-H), 7.27–8.67 (m, 8 H, aromatic H). Anal. ($C_{17}H_{16}N_4O_3$) C, H, N.

3-Amino-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (8u). To a mixture of 300 mg (0.9 mmol) of **6a** in 15 mL of CH_2Cl_2, 3.52 g (35 mmol) of MeOH containing 16.7% NH_3 was added, and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. Analogous work-up gave a residue, which was washed with Et_2O to give 204 mg [83%, mp 204.5–205.5 °C dec (lit.[8] 205–206 °C dec)] of **8u**.

1,3-Dihydro-7-nitro-5-phenyl-3-piperidino-2*H*-1,4-benzodiazepin-2-one (8v). To a solution of 40 mg (0.1 mmol) of **6c** in 2 mL of CH_2Cl_2, 100 mg (1.2 mmol) of piperidine was added, and the mixture was stirred for 5 min at room temperature. Analogous work-up gave a residue, which was washed with Et_2O to give 23 mg (57%, mp 205 °C dec) of **8v**. Recrystallization from AcOEt gave the pure sample: 10 mg (24.6%); mp 205–207 °C dec; IR (Nujol) 3250, 1720, 1708 cm^{-1}. Anal. ($C_{20}H_{20}N_4O_3$) C, H, N.

7-Chloro-1,5-dihydro-3-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (9j). A solution of 691 mg (2.3 mmol) of **8j** in a mixture of 20 mL of CH_2Cl_2, 10 mL of THF, and 14.4 g (23.2

mmol) of THF containing 5% CH_3NH_2 was stirred for 73.5 h at room temperature. After removal of solvent in vacuo the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to give a residue which was chromatographed on silica gel. The residue of fractions eluted with CH_2Cl_2 was collected and washed with isopropyl ether to give 574 mg (83%, mp 248–250 °C) of **9j**. Recrystallization from MeOH gave the pure sample: 387 mg (56%); mp 249–251 °C; IR (Nujol) 3200, 1690, 1665 cm^{-1}; NMR (Me_2SO-d_6) 3.72 (s, 3 H, OMe), 5.72 (s, 1 H, C_5-H), 6.43 (d, 1 H, J = 2.0 Hz, aromatic H-d_6), 7.00–7.83 (m, 7 H, aromatic H), 11.12 (br, 1 H, CONH). Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, Cl, N.

The residue of fractions eluted with CH_2Cl_2 containing 2% MeOH was collected and washed with isopropyl ether to give 81 mg (12%) of **8j**.

7-Chloro-1,5-dihydro-3-methylamino-2*H*-1,4-benzodiazepin-2-one (9s). A solution of 100 mg (0.3 mmol) of **8s** in 10 mL (1.6 mmol) of THF containing 5% CH_3NH_2 was stirred for 66 h at room temperature. Analogous work-up gave a residue, which was washed with isopropyl ether to give 31 mg (31%, mp 197–199 °C) and 21 mg (21%, mp 198–199 °C) of **9s**. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: mp 197.5–199 °C; IR (Nujol) 3470, 3225, 1675, 1647 cm^{-1}; NMR ($CDCl_3$) 2.87 (d, 3 H, J = 4 Hz, NMe), 5.37 (br, 1 H, NHMe), 5.62 (s, 1 H, C_5-H), 6.67 (d, 1 H, J = 1.5 Hz, aromatic C_6-H), 7.00–8.33 (m, 7 H, aromatic H), 11.42 (br, 1 H, CONH). Anal. ($C_{16}H_{14}ClN_3O$) C, H, Cl, N.

1,5-Dihydro-1-methyl-3-methylamino-6-nitro-2*H*-1,4-benzodiazepin-2-one (9t). A solution of 147 mg (0.5 mmol) of **8t** in a mixture of 6 mL of CH_2Cl_2, 96 mL of MeOH, and 1.81 g (4.6 mmol) of CH_2Cl_2 containing 7.8% CH_3NH_2 was stirred for 41 h at room temperature. The reaction mixture was washed with H_2O and dried over Na_2SO_4, filtered, and evaporated to give a residue which was washed with a mixture of AcOEt and isopropyl ether to give 123 mg (84%, mp 208–212.5 °C dec) of **9t**. Recrystallization from AcOEt gave the pure sample: mp 211–212.5 °C dec; IR (Nujol) 3280, 1656 cm^{-1}; NMR ($CDCl_3$) 2.78 (d, 3 H, J = 5.0 Hz, C_3-NMe), 3.17 (s, 3 H, CONMe), 5.65 (s, 1 H, C_5-H), 6.17 (d, 1 H, J = 1.5 Hz, aromatic C_6-H), 6.50–8.33 (m, 7 H, aromatic H). Anal. ($C_{17}H_{16}N_4O_3$) C, H, N.

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5-(Tetradecyloxy)-2-furancarboxylic Acid and Related Hypolipidemic Fatty Acid-Like Alkyloxyarylcarboxylic Acids[1]

Roger A. Parker,* Takashi Kariya, J. Martin Grisar, and Vladimir Petrow

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215.

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5-(Tetradecyloxy)-2-furancarboxylic acid (**91**, RMI 14 514) was found to lower blood lipids and to inhibit fatty acid synthesis with minimal effects on liver weight and liver fat content. This fatty acid-like compound represents a new class of hypolipidemic agent; it is effective in rats and monkeys. The compound resulted from discovery of hypolipidemic activity in certain β-keto esters, postulation and confirmation of the corresponding benzoic acids as active metabolites, and systematic exploration of the structure–activity relationships.

During our continued search for novel hypolipidemic agents, we discovered that methyl *p*-dodecylbenzoylacetate[2] (**3**) effectively lowered serum cholesterol and triglycerides in rats (cf. Table I). We also noted, however, that **3** caused an elevation of liver fat, particularly liver cholesterol, as well as liver weight. Further studies indicated that **3** and the corresponding benzoic acid **34** were incorporated to an appreciable degree into liver lipids of rats (triglycerides and cholesterol esters).[3] We subsequently prepared and evaluated a number of analogues to find an effective compound without these side effects. These compounds and their activities are listed in Tables I–V. (See Experimental Section for methods of evaluation.)

Systematic exploration of the structure–activity relationships of these fatty acid-like alkyloxyarylcarboxylic acids led to the preparation and selection of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**, RMI 14 514) for extended biological studies.[4]

Structure–Activity Relationships. Quite early during our investigation it was postulated[5] and subsequently shown that the β-keto esters are metabolized to the corresponding benzoic acids and that these are also active. Thus the benzoates **33**, **34**, **42**, **45**, and **59** have effects on lipids nearly identical with those of the corresponding β-keto esters **2**, **3**, **4**, **6**, and **13**, respectively. It is known that natural fatty acids are metabolized via β-oxidation to β-keto acids[6] and that this process is interrupted in unnatural fatty acid analogues in which a phenyl group is built into the alkyl chain.[7] It is therefore reasonable to postulate that β-keto esters of Table I are similarly metabolized to the corresponding benzoic acids as their co-