Quinazolines and 1,4-Benzodiazepines. 75.[1] 7-Hydroxyaminobenzodiazepines and Derivatives

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7-Nitro-substituted benzodiazepines were reduced with stannous chloride in a buffered system to the corresponding 7-hydroxyamino derivatives. These compounds were alkylated, acylated, and converted to nitroso and azoxy derivatives. The rearrangement of a hydroxyamine to an aminophenol and its oxidation to an aminoquinone are also exemplified. The results of the pharmacological screening for CNS effects are given.

The 7-hydroxyaminobenzodiazepines **2** may be expected to be short-lived or transient metabolites of the corresponding nitro compounds **1**. The metabolism of nitrazepam[2] (**1a**) and clonazepam[3] (**1f**) has been studied in detail but the hydroxyamines **2a** and **2f** have not been mentioned. Oelschläger and co-workers[4] reported on the polarographic reduction of nitrazepam and gave preparative evidence for the hydroxyamine **2a**. They did not isolate this compound but only characterized it in the form of its oxidation product, the azoxy derivative **4a**. This azoxy derivative also has been reported[5] to be a photoproduct of nitrazepam.

We found that the reduction of various 7-nitro-substituted benzodiazepines with stannous chloride dihydrate and sodium acetate trihydrate in methanol and tetrahydrofuran gave good yields of the corresponding hydroxyamines. Under our conditions further reduction to the amine and reduction of the imine was not observed. The azoxy compounds were minor by-products of the reduction. Compound **4c** was prepared by air oxidation or by treatment with activated manganese dioxide of the hydroxyamine **2c** (Scheme I). If a large amount of manganese dioxide was used, the nitroso derivative could be obtained as the major product. This means that in the presence of a large excess of oxidant the oxidation of the hydroxyamine to the nitroso compound is proceeding faster than the condensation to the azoxy derivative. While the nitroso compound **3** has limited stability and was not obtained in crystalline state, the nitrosotriazolobenzodiazepine **8** was crystalline and stable enough for pharmacological screening. Both nitroso derivatives were converted to the methylazoxy compounds **5** and **9**, respectively, by condensation with methylhydroxyamine. Acetylation of **2c** with acetic anhydride in pyridine followed by mild alkaline hydrolysis of the *O*-acetyl group led to the hydroxamic acid **14**. The corresponding trifluoroacetylhydroxamic acid **15** was prepared analogously but the acylation was carried out at lower temperature to avoid rearrangement to the aminophenol. These hydroxamic acids reacted with diazomethane to yield the *N*-methoxyamides **17** and **18**. The trifluoroacetate **18** was very susceptible to base-catalyzed hydrolysis. The compound itself was a strong enough base to effect partial hydrolysis of **18** on silica gel to the methoxyamine **20**. The latter was therefore readily obtained by treatment of **18** with methanol and triethylamine.

Alkylation of the hydroxyamine **2c** with potassium *tert*-butoxide and methyl iodide in dimethylformamide led to a complex mixture which after chromatography afforded the crystalline 3-methyl derivative **12** and the noncrystallizable compound **13**. Reaction of **2c** with trifluoroacetic anhydride and pyridine in refluxing methylene chloride followed by alkaline hydrolysis afforded the aminophenol **16** which was oxidized by Fremy's salt to the aminoquinone **19** (Scheme II).

Biological Activity. The compounds were tested orally in mice for the CNS effects of benzodiazepines according to previously described procedures.[2b,6] The results of the inclined screen test, the footshock test, and the antagonism against pentylenetetrazole are given in Table I. The substitution of the nitro group by a hydroxyamino group generally results in some loss of activity. This loss is particularly dramatic for the triazolobenzodiazepine **7** but less significant for the hydroxyamines **2c**, **2b**, **2d**, and **2e** which retain high activity in the metrazole test. Compound **2c** is unique in that it shows good activity in all three tests at a level similar to that of the nitro compound. The assumption that fusion of a triazolo ring to the benzodiazepine system will result in higher potency is apparently not valid for these compounds. The activity decreases when the hydroxyamine **2c** is converted to the methylazoxy

Scheme I

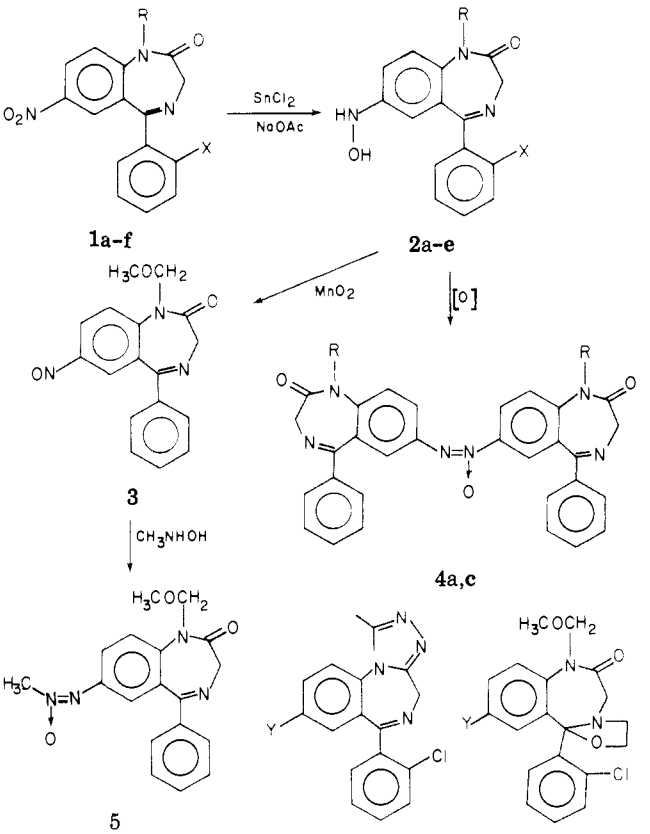


Table I. Pharmacological Data

Compd	ED_{50}, mg/kg po		
	Inclined screen	Footshock anti-fighting	Anti-pentylene-tetrazole
Diazepam	25	10	1.4
1a (nitrazepam)	15	5	0.7
2c	25	5	1.57
2b	400	100	0.77
2d	500	12.5	2.6
2e	500	25	0.76
4c	>400	NT	>800
5	150	50	60
7	400	10	74
8	30	10	4
9	50	10	1.65
10	60	10	0.9
11	350	25	3.1
12	400	100	>100
14	300	50	2.25
15	25	10	4
16	>400	>100	>800
17	>100	100	1.4
18	75	5	2.8
19	>100	>100	>800
20	200	100	>100

derivative **5** but increases when the same transformation is done with the triazolo compound **7**. Among the derivatives of **2c** the hydroxyamic acids **14** and **15** and the methylated analogues **17** and **18** exhibited considerable activity. The azoxy compound **4c**, the aminophenol **16**, and its oxidation product **19** were devoid of CNS effects.

Experimental Section

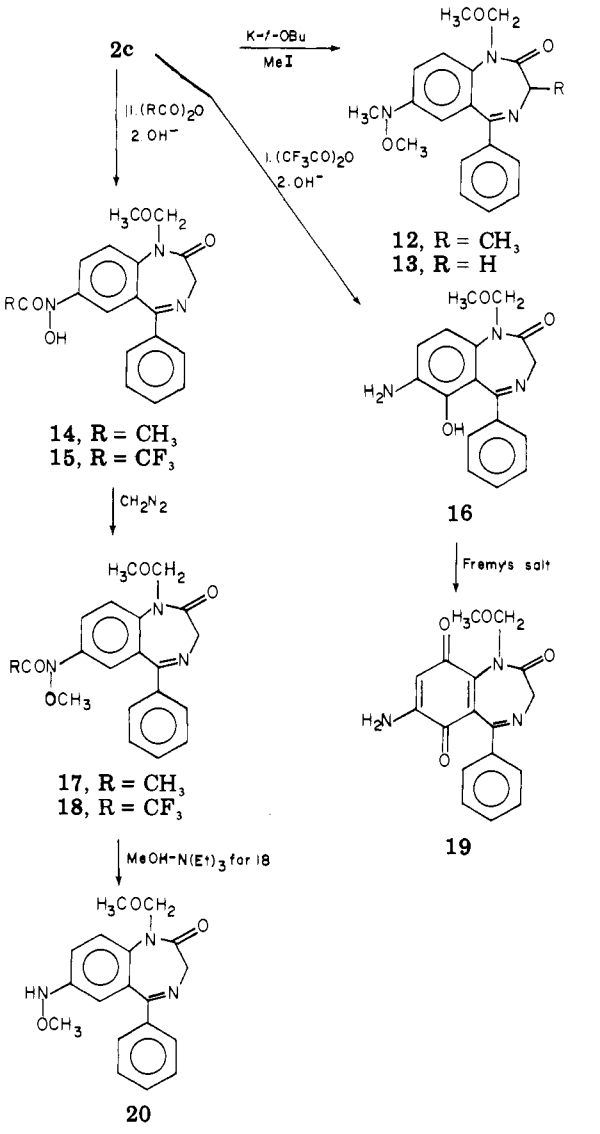
Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotomether. NMR spectra were recorded with a Varian T-60 instrument with Me_4Si as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Merck silica gel (70–325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

1,3-Dihydro-7-hydroxyamino-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (2c). A mixture of 33 g (0.1 mol) of **1c**,[7] 1 l. of THF, 1 l. of MeOH, 113 g (0.5 mol) of $SnCl_2{\cdot}2H_2O$, and 136 g (1 mol) of $NaOAc{\cdot}3H_2O$ was stirred at room temperature for 6 h under an atmosphere of nitrogen. The inorganic salts were separated by filtration over Celite. The filtrate was evaporated and the residue was partitioned between CH_2Cl_2 and 1 N NaOH solution. The CH_2Cl_2 layer was washed with H_2O, dried, and evaporated. Crystallization of the residue from CH_2Cl_2–Et_2O yielded 22 g (70%) of light yellow product with mp 168–170 °C: uv λ max 245 nm (ε 28900), 338 (2100); ir ($CHCl_3$) 3550 (OH), 3300 (NH), 1685 cm^{-1} (NCO); NMR ($CDCl_3$) δ 3.32 (s, 3, OCH_3), 3.78 (d, 1) and 4.73 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.90 (d, 1) and 5.32 (d, 1) (AB system, J = 10 Hz, NCH_2O), 6.77 (d, 1, J = 2.5 Hz, C_6-H), 7.10 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2.5 Hz, C_8-H), ~6.8 (br s, 2, –NHOH), 7.2–7.8 ppm (m, 6, C_6H_5 + C_9-H). Anal. ($C_{17}H_{17}N_3O_3$) C, H, N.

In the same manner were prepared **1,3-dihydro-7-hydroxyamino-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (2b)** [mp 211–213 °C (from CH_2Cl_2–EtOH); yield 49%. Anal. ($C_{16}H_{15}N_3O_2$) C, H, N], **1,3-dihydro-5-(2-fluorophenyl)-7-hydroxyamino-1-methyl-2*H*-1,4-benzodiazepin-2-one (2d)** [mp 228–230 °C dec (from THF–EtOH); yield 52%. Anal. ($C_{16}H_{14}N_3O_2F$) C, H, N], and **5-(2-chlorophenyl)-1,3-dihydro-7-hydroxyamino-1-methoxymethyl-2*H*-1,4-benzodiazepin-2-one (2e)** [mp 205–208 °C dec (from THF–2-PrOH); yield 90%. Anal. ($C_{17}H_{16}ClN_3O_3$) C, H, N].

1,3-Dihydro-7-hydroxyamino-5-phenyl-2*H*-1,4-benzodiazepin-2-one (2a). A mixture of 16.8 g of **1a**, 500 ml of THF, 250 ml of MeOH, 56 g of $SnCl_2{\cdot}2H_2O$, and 68 g of $NaOAc{\cdot}3H_2O$ was stirred at room temperature under an atmosphere of N_2 for 24 h. THF (1 l.) and 15 ml of concentrated NH_3 were then added. The inorganic salts were removed by filtration through Celite. The filtrate was evaporated. The solid residue was stirred with 100 ml of CH_2Cl_2 and 250 ml of H_2O for 20 min under nitrogen. The insoluble crystals were collected to leave 10 g (74%) of light yellow material.

Scheme II



For analysis it was recrystallized from EtOH–CH_2Cl_2: mp 186–187 °C. Anal. ($C_{15}H_{13}N_3O_2$) C, H, N.

1,3-Dihydro-1-methoxymethyl-7-nitroso-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3). Activated MnO_2 (30 g) was added to a solution of 3.1 g (0.01 mol) of **2c** in 200 ml of CH_2Cl_2. After stirring for 10 min at room temperature, the inorganic material was filtered off and the filtrate was evaporated to leave an oil with a greenish tint. Since crystallization attempts were unsuccessful the material was purified by chromatography over 50 g of silica gel using 5% (v/v) EtOAc in CH_2Cl_2. The thin-layer chromatographically pure fractions (1.7 g, 55%) still did not crystallize. The compound was characterized by NMR: NMR ($CDCl_3$) δ 3.42 (s, 3, OCH_3), 3.87 (d, 1) and 4.90 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.92 (d, 1) and 5.47 (d, 1) (AB system, J = 10 Hz, NCH_2O), 7.2–7.8 (m, 6, C_6H_5 and C_8-H), 7.90 (d, 1, J = 9 Hz, C_9-H), 8.11 ppm (d, 1, J = 2 Hz, C_6-H).

7,7′-Azoxydi(1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) (4c). A solution of 9.3 g (0.03 mol) of **2c** in 300 ml of CH_2Cl_2 was stirred with 20 g of activated MnO_2 for 18 h. The MnO_2 was removed by filtration over Celite. The filtrate was evaporated and the residue was crystallized from CH_2Cl_2–Et_2O–hexane to yield 4.8 g (53%) of yellow product: mp 240–242 °C after recrystallization from CH_2Cl_2–hexane; uv λ max 220 nm (ε 44400), 260 (31600), 352 (20550), infl 388 (11000); NMR ($CDCl_3$) δ 3.42 (s, 6, OCH_3), 3.85 (br d, 2) and 4.88 (br d, 2) (AB

system, J = 10 Hz, C_3-H), 4.95 (d, 2) and 5.48 (d, 2) (AB system, J = 10 Hz, NCH_2O), 7.2–8.6 ppm (m, 16, aromatic H); MS m/e 602 (M^+), 586 ($M^+ - 16$), 576, 560, 542, 307, 295, 265, 248, 234, 221, 205, 91. Anal. ($C_{34}H_{30}N_6O_5$) C, H, N.

This compound was also found in the mother liquors of the hydroxyamine **2c** and was also formed by air oxidation of **2c**.

1,3-Dihydro-7-(*N*-methyl-*N*-oxyazo)-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (5). A mixture of 9.3 g (0.03 mol) of **2c**, 300 ml of CH_2Cl_2, and 100 g of activated MnO_2 was stirred for 10 min at room temperature. The reaction mixture was filtered through Celite into a mixture of 7.5 g (0.09 mol) of methylhydroxyamine hydrochloride, 15 g of NaOAc, and 100 ml of EtOH. The CH_2Cl_2 was partially evaporated under reduced pressure and the remaining solution was heated on the steam bath for 10 min. The residue obtained after complete evaporation was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ solution. The organic layer was dried and evaporated. The residue was chromatographed over 250 g of silica gel with 10% (v/v) EtOAc in CH_2Cl_2. Crystallization of the pure fractions from Et_2O–hexane yielded 3.8 g (37.5%) of colorless product with mp 110–115 °C: uv λ max 225 nm (ε 28040), max 249 (25400), infl 310 (3750); NMR ($CDCl_3$) δ 3.38 (s, 6, OCH_3, NCH_3), 3.84 (d, 1) and 4.86 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.9 (d, 1) and 5.43 (d, 1) (AB system, J = 10 Hz, NCH_2O), 7.15–7.7 (m, 5, C_6H_5), 7.75 (d, 1, J = 9 Hz, C_9-H), 8.02 (d, 1, J = 2 Hz, C_6-H), 8.25 ppm (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_8-H). Anal. ($C_{18}H_{18}N_4O_3$) C, H, N.

6-(2-Chlorophenyl)-8-hydroxyamino-1-methyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (7). A mixture of 3.55 g (0.01 mol) of 6-(2-chlorophenyl)-1-methyl-8-nitro-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**6**),[8] 200 ml of THF, 100 ml of MeOH, 13.6 g of $NaOAc·3H_2O$, and 12 g of $SnCl_2·2H_2O$ was stirred at room temperature for 1 h under N_2 atmosphere. After addition of 5 ml of concentrated NH_4OH, the inorganic material was washed with 500 ml of CH_2Cl_2 containing 20% (v/v) of EtOH. The filtrate was evaporated and the residue was stirred with 100 ml of H_2O and 30 ml of CH_2Cl_2. The crystalline material was collected and washed successively with H_2O, EtOH, and Et_2O to leave 2.9 g (85%) of product. For analysis it was recrystallized from THF–MeOH: mp 276–278 °C dec; uv λ infl 210 nm (ε 29800), max 243 (23300), sh 270 (11800), max 330 (2000). Anal. ($C_{17}H_{14}ClN_5O$) C, H, N.

6-(2-Chlorophenyl)-1-methyl-8-nitroso-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (8). Activated MnO_2, 20 g, was added to a suspension of 2 g of **7** in 1 l. of CH_2Cl_2. After stirring for 3 h at room temperature the MnO_2 was separated by filtration over Celite. The filtrate was evaporated and the residue was crystallized from CH_2Cl_2–Et_2O to leave 1 g (50%) of product with mp 190–195 °C dec. For analysis it was recrystallized from EtOH–Et_2O: uv λ infl 215 nm (ε 25700), max 247 (14700), 291 (10600), 315 (9990); NMR ($CDCl_3$) δ 2.66 (s, 3, CH_3), 4.16 (d, 1) and 5.53 (d, 1) (AB system, J = 13 Hz, C_4-H), 7.2–8.1 ppm (m, 7, aromatic H). Anal. ($C_{17}H_{12}ClN_5O$) C, H, N.

6-(2-Chlorophenyl)-1-methyl-8-(*N*-methyl-*N*-oxyazo)-4*H*-*s*-triazolo[4,5-*a*][1,4]benzodiazepine (9). A mixture of 1 g of **8**, 1 g of methylhydroxyamine, 1.5 g of NaOAc, and 30 ml of EtOH was heated to 40–50 °C for 5 min. The EtOH was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 solution. The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was chromatographed over 30 g of silica gel using 10% (v/v) EtOH in CH_2Cl_2. Clean fractions were combined and evaporated. Crystallization from EtOAc yielded 0.7 g (63%) of product. Since no solvent-free crystals were obtained with a variety of solvents, the product was characterized as a solvate. Recrystallization from 2-PrOH yielded crystals containing, according to NMR spectrum and analysis, 0.25 mol of solvent with mp 160–165 °C: uv λ max 234 nm (ε 29200), infl 265 (13800); NMR ($CDCl_3$) δ 2.66 (s, 3, CH_3), 3.45 (s, 3, NCH_3), 4.16 (d, 1) and 5.56 (d, 1) (AB system, J = 13 Hz, C_4-H), 7.2–7.8 (m, 5, aromatic H), 8.0 (d, 1, J = 2.5 Hz, C_7-H), 8.44 ppm (q, 1, J_{AB} = 9 Hz, J_{AX} = 2.5 Hz, C_9-H). Anal. [$C_{18}H_{15}ClN_6O·0.25$(2-PrOH)] C, H, N.

11b-(2-Chlorophenyl)-7-methoxymethyl-10-nitro-2,3,5,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(7*H*)-one (10). Potassium *tert*-butoxide, 1.25 g (0.011 mol), was added to a solution of 3.6 g (0.01 mol) of 11b-(2-chlorophenyl)-10-nitro-2,3,5,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(7*H*)-one[9] in 50 ml of DMF cooled to −20 °C. After stirring for 5 min under N_2, the mixture was further cooled to −40 °C when 1 ml (0.0125 mol) of chlorodimethyl ether was added. The temperature was allowed to reach −20 °C. H_2O was added and the precipitated crystals were collected and recrystallized from EtOH to leave 2.6 g (65%) of product with mp 139–141 °C. Anal. ($C_{19}H_{18}ClN_3O_5$) C, H, N.

11b-(2-Chlorophenyl)-10-hydroxyamino-7-methoxymethyl-2,3,5,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(7*H*)-one (11). A mixture of 4 g (0.01 mol) of **10**, 100 ml of THF, 50 ml of MeOH, 13.6 g of $NaOAc·3H_2O$, and 11.3 g of $SnCl_2·2H_2O$ was stirred under N_2 for 4 h. CH_2Cl_2 (300 ml) and 15 ml of concentrated NH_4OH were added. The inorganic material was removed by filtration through Celite. The filtrate was washed with 1 N NaOH solution, dried, and evaporated. The residue was chromatographed over 75 g of silica gel with EtOAc–CH_2Cl_2 (1:1). Crystallization of the combined clean fractions from Et_2O yielded 1 g (26%) of product with mp 160–162 °C dec: uv λ max 254 nm (ε 11400), infl 305 (2200). Anal. ($C_{19}H_{20}ClN_3O_4$) C, H, N.

1,3-Dihydro-1-methoxymethyl-3-methyl-7-(*N*-methyl-*N*-methoxyamino)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (12) and 1,3-Dihydro-1-methoxymethyl-7-(*N*-methyl-*N*-methoxyamino)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (13). Potassium *tert*-butoxide, 7.5 g (0.066 mol), was added to a solution of 6.2 g (0.02 mol) of **2c** in 120 ml of DMF cooled to 0 °C. With stirring under N_2 10 g (0.07 mol) of CH_3I was added. After stirring for 30 min at room temperature, the reaction mixture was diluted with H_2O and extracted with C_6H_6. The organic phase was washed with H_2O, dried, and evaporated. Chromatography of the remaining oil on 200 g of silica gel with 10% (v/v) EtOAc in CH_2Cl_2 and crystallization of clean fractions from Et_2O yielded 1.1 g (15.5%) of product with mp 148–150 °C. For analysis it was recrystallized from MeOH–H_2O: uv λ max 240 nm (ε 27650), 330 (2500); NMR ($CDCl_3$) δ 1.73 (d, 3, J = 6.5 Hz, $CHCH_3$), 3.02 (s, 3, NCH_3), 3.36 (s, 3, OCH_3), 3.65 (s, 3, $NOCH_3$), 3.87 (q, 1, J = 6.5 Hz, C_3-H), 5.0 (d, 1) and 5.43 (d, 1) (AB system, J = 10 Hz, NCH_2O), 6.9 (d, 1, J = 2.5 Hz, C_6-H), 7–7.8 ppm (m, 7, aromatic H). Anal. ($C_{20}H_{23}N_3O_3$) C, H, N.

Fractions containing a slightly slower moving compound were also combined and evaporated to leave 0.8 g (12%) of **13** which resisted all attempts to crystallize: NMR ($CDCl_3$) δ 3.0 (s, 3, NCH_3), 3.36 (s, 3, OCH_3), 3.64 (s, 3, $NOCH_3$), 3.88 (d, 1) and 4.82 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.95 (d, 1) and 5.4 (d, 1) (AB system, J = 10 Hz, NCH_2O), 6.85 (d, 1, J = 2.5 Hz, C_6-H), 7–7.8 ppm (m, 7, aromatic H).

1,3-Dihydro-7-(*N*-hydroxyacetamino)-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (14). A mixture of 9.3 g (0.03 mol) of **2c**, 100 ml of pyridine, and 15 ml of Ac_2O was allowed to sit at room temperature for 16 h. The reagents were evaporated, at the end azeotropically with xylene. The residue was dissolved in 100 ml of MeOH. The solution was cooled in ice–H_2O when 100 ml of 1 N NaOH solution was added. After standing at room temperature for 10 min, the reaction mixture was acidified with solid CO_2 and was extracted with CH_2Cl_2. The extracts were dried and evaporated. Crystallization of the residue from ether yielded 4.8 g (45%) of yellow product with mp 205–208 °C dec. For analysis it was recrystallized from CH_2Cl_2–2-PrOH: uv λ infl 215 nm (ε 26600), max 253 (26150), 317 (2350); NMR ($CDCl_3$ + Me_2SO) δ 2.27 (s, 3, $COCH_3$), 3.32 (s, 3, OCH_3), 3.83 (d, 1) and 4.70 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.94 (d, 1) and 5.35 (d, 1) (AB system, J = 10 Hz, NCH_2O), 7.2–7.8 (m, 7, aromatic H), 7.93 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_8-H), 10.3 ppm (s, 1, OH). Anal. ($C_{19}H_{19}N_3O_4$) C, H, N.

1,3-Dihydro-7-(*N*-hydroxytrifluoroacetamino)-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (15). $(CF_3CO)_2O$ (10 ml) and 20 ml of pyridine was added to a solution of 9.3 g (0.03 mol) of **2c** in 500 ml of CH_2Cl_2 cooled to −50 °C. Cooling was discontinued and the mixture was stirred for 5 min. When the temperature rose to −30 °C the reaction mixture was quenched with 20 ml of MeOH and shaken with saturated $NaHCO_3$ solution. The organic phase was separated, dried, and evaporated. Crystallization of the residue from Et_2O–petroleum ether yielded 9.0 g (75%) of tan product with mp 175–178 °C dec. Recrystallization from CH_2Cl_2–MeOH–Et_2O gave 6.6 g (55%) of off-white crystals with mp 183–185 °C dec: uv λ max 219 nm (ε

27 050), 255 (23 050), infl 275 (18 800), infl 320 (2250); ir (KBr) 1680 (NCO), 1660 cm^{-1} (-$NCOCH_3$); NMR (Me_2SO) δ 3.17 (s, 3, OCH_3), 3.85 (d, 1) and 4.63 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 5.08 (d, 1) and 5.33 (d, 1) (AB system, J = 10 Hz, -NCH_2O), 7.2–8.0 (m, 8, aromatic H), 11.8 ppm (s, 1, -OH). Anal. ($C_{19}H_{16}F_3N_3O_4$) C, H, N.

7-Amino-1,3-dihydro-6-hydroxy-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (16). $(CF_3CO)_2O$ (10 ml) and 10 ml of pyridine were added to a solution of 9.3 g (0.03 mol) of **2c** in 300 ml of CH_2Cl_2. After refluxing for 1 h the reaction mixture was evaporated. The residue was dissolved in 150 ml of MeOH and 150 ml of aqueous 1 N NaOH. The MeOH was evaporated under reduced pressure after sitting for 1 h at room temperature. The remaining aqueous solution was extracted twice with Et_2O. The Et_2O extracts were washed back with 1 N NaOH. The washings were combined with the original hydroxide solution and were buffered to pH ~8 by addition of AcOH and $NaHCO_3$ solution. The precipitated material was extracted with CH_2Cl_2. The extracts were dried and evaporated. Crystallization of the residue from CH_2Cl_2 gave 5.1 g (55%) of yellow crystals with mp 202–204 °C. The analytical sample was recrystallized from CH_2Cl_2–MeOH–Et_2O: mp 204–206 °C; uv λ max 248 nm (ε 25 000), 345 (2300); NMR (Me_2SO) δ 3.04 (s, 3, OCH_3), 3.83 (d, 1) and 4.43 (d, 1) (AB system, J = 10 Hz, C_3-H), 5.01 (s, 2, NCH_2O), 6.77 (d, 1) and 6.95 (d, 1) (AB system, J = 9 Hz, C_8-H and C_9-H), 7.1–7.6 ppm (m, 5, C_6H_5), exchangeable protons and water appear as broad signals at 3.34 and 5.83. Anal. ($C_{17}H_{17}N_3O_3$) C, H, N.

1,3-Dihydro-7-(*N*-methoxyacetamino)-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (17). Potassium *tert*-butoxide, 1.2 g (0.0106 mol), was added to a solution of 3.6 g (0.01 mol) of **14** in 40 ml of DMF cooled to -10 °C. After stirring for 10 min 1.5 g (0.0106 mol) of CH_3I was added and stirring was continued for 15 min at room temperature. The solvent was partially evaporated under reduced pressure. The remaining warm solution was diluted with H_2O and crystallized by seeding and cooling. Seeds were obtained by previous chromatographic purification over silica gel using 20% (v/v) EtOAc in CH_2Cl_2. The crystals were collected and recrystallized twice from CH_2Cl_2–Et_2O–hexane to leave 1.7 g (46%) of light yellow product with mp 125–128 °C; uv λ infl 215 nm (ε 31 000), max 249 (26 400), 314 (2 200); NMR ($CDCl_3$) δ 2.26 (s, 3, $COCH_3$), 3.36 (s, 3, OCH_3), 3.67 (s, 3, $NOCH_3$), 3.87 (d, 1) and 4.83 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.91 (d, 1) and 5.40 (d, 1) (AB system, J = 10 Hz, NCH_2O), 7.2–7.8 ppm (m, 8, aromatic H). Anal. ($C_{20}H_{21}N_3O_4$) C, H, N.

1,3-Dihydro-1-methoxymethyl-7-(*N*-methoxytrifluoroacetamino)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (18). CH_2N_2 in Et_2O was added to a solution of 2 g (0.005 mol) of **15** in 40 ml of CH_2Cl_2 and 20 ml of MeOH. After no more gas evolution was noticed (15 min) the mixture was evaporated and the residue was chromatographed over 60 g of silica gel using 10% (v/v) EtOAc in CH_2Cl_2. Crystallization of the pure fractions from Et_2O–hexane yielded 1.1 g (53%) of product with mp 110–112 °C: uv λ max 220 nm (ε 28 450), 254 (23 000), sh 315 (2200); NMR ($CDCl_3$) δ 3.40 (s, 3, OCH_3), 3.73 (s, 3, $NOCH_3$), 3.86 (d, 1) and 4.90 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.92 (d, 1) and 5.47 (d, 1) (AB system, J = 10 Hz, NCH_2O), 7.2–8.0 ppm (m, 8, aromatic H). Anal. ($C_{20}H_{18}F_3N_3O_4$) C, H, N.

With EtOAc a second compound was eluted. It was crystallized from Et_2O–hexane to yield 0.3 g (19%) of light yellow crystals with mp 147–149 °C. It was found to be identical with compound **20**.

7-Amino-1-methoxymethyl-5-phenyl-1,3-dihydro-2*H*,6*H*,-9*H*-1,4-benzodiazepine-2,6,9-trione (19). Wet Fremy's salt (20 g) suspended in 50 ml of H_2O containing 0.3 g of NaH_2PO_4 was added to a solution of 2.2 g (0.007 mol) of **16** in 60 ml of MeOH and 30 ml of CH_2Cl_2. After stirring at room temperature for 2 h, the mixture was partitioned between CH_2Cl_2 and H_2O. The red organic layer was separated, dried, and evaporated. The residue was chromatographed over 60 g of silica gel using 20% (v/v) EtOAc in CH_2Cl_2. Crystallization of the pure fractions from CH_2Cl_2–Et_2O yielded 0.4 g (17%) of purple product. For analysis it was recrystallized from CH_2Cl_2–MeOH–Et_2O: mp 219–220 °C dec; uv λ max 215 nm (ε 26 600), 257 (15 150), 323 (7080), 510 (1400); NMR (Me_2SO) δ 2.95 (s, 3, OCH_3), 4.33 (d, 1) and 4.65 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 5.05 (d, 1) and 5.4 (d, 1) (AB system, J = 10 Hz, NCH_2O), 5.64 (s, 1, C_8-H), 7.24 (br s, 2, NH_2), 7.36 ppm (m, 5, C_6H_5). Anal. ($C_{17}H_{15}N_3O_4$) C, H, N.

1,3-Dihydro-7-methoxyamino-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (20). $(Et)_3N$ (1 ml) was added to a solution of 1 g of **18** in 20 ml of MeOH. After refluxing for 10 min the solvents were removed under reduced pressure and the residue was crystallized from Et_2O to leave 0.65 g (84%) of light yellow product with mp 147–149 °C: uv λ max 242 nm (ε 29 500), infl 265 (15 300), 335 (2500); NMR ($CDCl_3$) δ 3.35 (s, 3, OCH_3), 3.68 (s, 3, $NOCH_3$), 3.86 (d, 1) and 4.80 (d, 1) (AB system, J = 10.5 Hz, C_3H), 4.93 (d, 1) and 5.37 (d, 1) (AB system, J = 10 Hz, NCH_2O), 6.77 (d, 1, J = 2.5 Hz, C_6-H), 7.08 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2.5 Hz, C_8-H), 7.2–7.8 ppm (m, 7, C_6H_5, C_9-H, NH). Anal. ($C_{18}H_{19}N_3O_3$) C, H, N.

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