Synthesis of Novel 4-Amino-1,4-benzodiazepine-2,5-diones for Anticonvulsant Testing [1]

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A series of novel 4-amino-1,4-benzodiazepine-2,5-diones was synthesized *via* two pathways. The first method involved reductive alkylation of unsymmetrical hydrazines with glyoxylic acid, followed by Fisher esterification. The resulting *N*-aminoglycinate ethyl ester was subsequently *o*-nitrobenzoylated, reduced, and thermally cyclized to obtain 4-dialkylaminobenzodiazepinones. In the second method methylhydrazine was acetylated at N_α then benzoylated at N_β to give 1,2-diacylhydrazines. Alkylation with ethyl bromoacetate and reduction of the nitro group, followed by thermal cyclization yielded 4-acetamidobenzodiazepinones. All title compounds were evaluated in mice in MES seizure and sc Met seizure threshold tests for anticonvulsant activity, and in the rotorod test for neurotoxicity. Activity and toxicity were both minimal.

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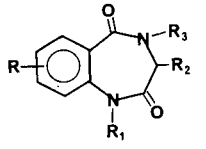
It has been reported [2] that the extreme lipophilicity of Diazepam® causes it to enter the brain with great rapidity, however, this same lipophilicity causes its rapid redistribution from the brain, thus decreasing the duration of action. A great deal of SAR studies done in the benzodiazepine class has therefore been directed towards optimizing the physicochemical properties of the molecule without sacrificing biological activity. These studies, however, have been limited to benzodiazepines of the general structure **1** because such compounds were generally active and were readily prepared [3]. More recently, 3-amino-2,4-quinazolinediones **2** have been shown [4] to be active against MES and sc Met induced seizures. It was therefore of interest to investigate the seven-membered ring analogs of **2**. The title compounds differ from compounds **1** in that R_3 is an amino rather than an alkyl group, thus extending the exploration of benzodiazepine SAR.



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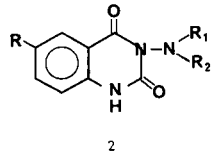

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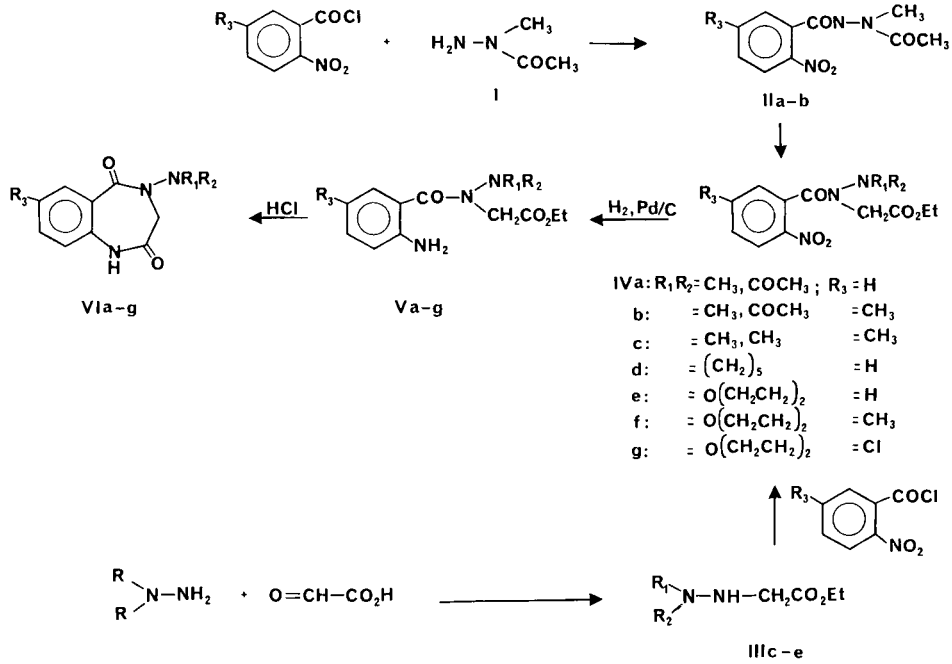
Scheme I



The synthetic pathway used in obtaining the title benzodiazepines is summarized in Scheme I. The key intermediates **IVa-g** were prepared *via* two methods depending on the substitution of the hydrazine. For monosubstituted hydrazines the method described by Peet [5] was employed. By first acetylating methylhydrazine at N_α to obtain the derivative **I**, the subsequent *o*-nitrobenzoylation was directed to the desired N_β position. Alkylation of the 1,2-diacylhydrazines **IIa-b** with ethyl bromoacetate and sodium hydride as the base produced **IVa-b** in moderate yields. In the case of unsymmetrical disubstituted hydrazines, reductive alkylation by glyoxylic acid with sodium cyanoborohydride according to the method of Borch [6], followed by Fisher esterification, afforded ethyl *N*-aminoglycinates **IIIc-e**. Reaction of **IIIc-e** with an appropriate benzoyl chloride gave the key intermediates **IVc-g** in good yields. Attempts to benzoylate the corresponding alaninates in a similar manner failed probably due to steric factors. Also, an attempt to obtain **IVf** from **IIIe** and 5-methyl-2-nitrobenzoic acid in the presence of silicon tetrachloride as a coupling reagent [7] resulted in isolation of starting materials. The key intermediates **IVa-g** were reduced by catalytic hydrogenation to the corresponding amines **Va-g** and cyclized by refluxing the hydrochloride salts in pyridine to obtain the title benzodiazepines. A one step synthesis of 1,4-benzodiazepinones has been previously described [8,9] by heating an isatoic anhydride with ethyl glycinate hydrochloride in pyridine. However, when 5-chlorosatoic anhydride and **IIIe** hydrochloride were refluxed in pyridine for 10 hours in an attempt to prepare **VIg**, only a low yield of white powder (mp 196-199°) was isolated. It was determined by nmr to be the corresponding *o*-ureidobenzoic acid **VII**, produced by "abnormal" ring opening (Scheme II). In a second attempt a catalytic amount of 4-dimethylaminopyridine (DMAP) was added to favor the desired "normal" ring opening [10] that would lead to the desired product, but the catalyst was ineffectual. The properties of the key intermediates and title compounds are summarized in Tables I and II respectively.

Scheme II

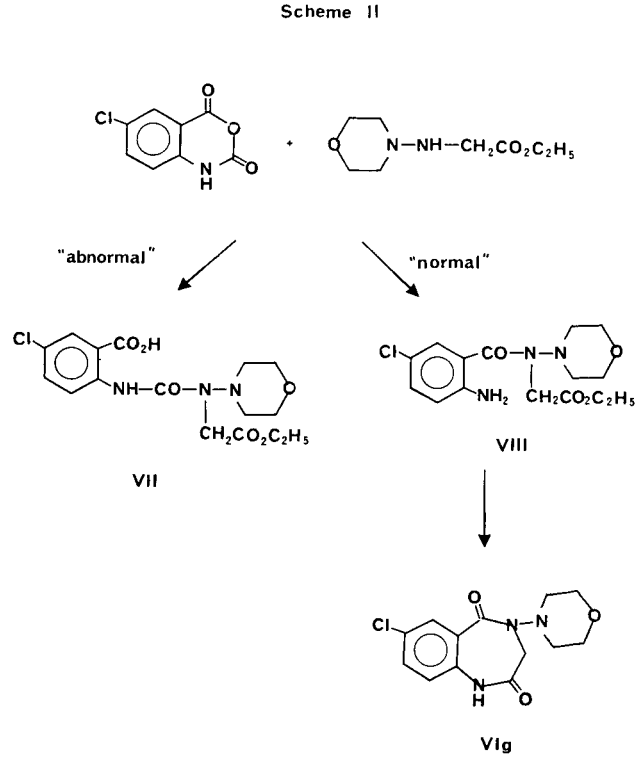


Table I

Properties of Ethyl *N*-(*o*-Nitrobenzoyl)-*N*-aminoglycinates **IV**

Compound	R_1	R_2	R_3	mp, °C	Yield, %	Formula	Analysis, % Calcd./Found C	H	N
IVa	CH_3	$COCH_3$	H	109-111 [a]	65	$C_{14}H_{17}N_3O_6$	52.01	5.30	13.00
							52.05	5.45	13.04
IVb	CH_3	$COCH_3$	CH_3	90-92 [b]	67	$C_{15}H_{19}N_3O_6$	53.41	5.68	12.46
							53.17	5.72	12.44
IVc	CH_3	CH_3	CH_3	94-96 [c]	33	$C_{14}H_{19}N_3O_5$	54.36	6.19	13.58
							54.37	6.27	13.56
IVd [d]	$(CH_2)_5$		H	124-126 [b]	80	$C_{16}H_{23}N_3O_3$	62.93	7.59	13.76
							63.17	7.59	13.86
IVe	$O(CH_2CH_2)_2$		H	96-98 [c]	73	$C_{15}H_{19}N_3O_6$	53.41	5.68	12.46
							53.44	5.43	12.35
IVf	$O(CH_2CH_2)_2$		CH_3	137-139 [b]	64	$C_{16}H_{21}N_3O_6$	54.70	6.02	11.96
							54.70	6.08	11.95
IVg	$O(CH_2CH_2)_2$		Cl	145-147 [b]	55	$C_{15}H_{18}ClN_3O_6$	48.46	4.88	11.30
							48.55	4.80	11.37

[a] Ethyl acetate-hexane. [b] 95% Ethanol. [c] 95% Ethanol-water. [d] *o*-Aminobenzoyl intermediate obtained by catalytic reduction of corresponding nitro compound.

Table II

Properties of 4-Amino-1,4-Benzodiazepine-2,5-diones **VI**

Compound	R_1	R_2	R_3	mp, °C	Yield, %	Formula	Analysis, % Calcd./Found C	H	N
VIa	CH_3	$COCH_3$	H	168-170 [a]	49	$C_{12}H_{13}N_3O_3$	58.29	5.30	16.99
							58.30	5.60	17.24
VIb	CH_3	$COCH_3$	CH_3	207-209 [a]	70	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.08
							59.54	5.73	16.08
VIc	CH_3	CH_3	CH_3	205-207 [b]	55	$C_{12}H_{15}N_3O_2$	61.79	6.48	18.01
							61.73	6.61	18.03
VId	$(CH_2)_5$		H	196-198 [c]	45	$C_{14}H_{17}N_3O_2$	64.85	6.61	16.20
							64.80	6.53	16.23
VIe	$O(CH_2CH_2)_2$		H	220-221 [a]	54	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.08
							59.87	5.84	16.37
VIf	$O(CH_2CH_2)_2$		CH_3	202-204 [a]	64	$C_{14}H_{18}N_3O_{3.5}$ [d]	59.14	6.38	14.78
							59.54	6.40	14.86
VIg	$O(CH_2CH_2)_2$		Cl	204-206 [a]	63	$C_{13}H_{14}ClN_3O_3$	52.80	4.77	14.21
							52.76	4.87	14.27

[a] 95% Ethanol. [b] Ethanol/water. [c] Ethyl acetate. [d] Hemihydrate.

Compounds **VIa-g** were evaluated in the maximal electroshock (MES) seizure and pentylenetetrazole (sc Met) seizure threshold tests for anticonvulsant activity in male Carworth Farms No. 1 mice by reported procedures [11]. Neurotoxicity was also determined for these compounds by the rotorod test [11]. The benzodiazepines tested were generally inactive against MES seizures at doses up to 300 mg/kg. Compounds **VIa** and **VIg** exhibited minimal anticonvulsant activity (300 mg/kg) against sc Met induced seizures. The most potent analog of the series was compound **VIc**. It exhibited activity at 30 mg/kg against seizures induced by pentylenetetrazole. Of some significance is the fact that lack of activity was accompanied by absence of neurotoxicity for most of these compounds. This appears to suggest that the title benzodiazepines were devoid of sufficient lipid character to permit penetration of the blood brain barrier.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as internal reference. Elemental analyses were performed by Micanal, Tucson, Arizona.

2-(*o*-Nitrobenzoyl)-1-acetyl-1-methylhydrazine (**IIa**).

A mixture consisting of 53.5 g (0.32 mole) of *o*-nitrobenzoic acid and 230 ml (3.2 mole) of thionyl chloride was refluxed until evolution of hydrogen chloride fumes ceased, as indicated by wet litmus (5 hours). Excess thionyl chloride was distilled off and the residue was dissolved in 150 ml of dry pyridine. To the ice-cooled solution was added 28.6 g (0.32 mole) of 1-acetyl-1-methylhydrazine (**I**), dropwise and with stirring. The reaction mixture was stirred at room temperature overnight under nitrogen, then refluxed for 2 hours. After cooling to room temperature the solution was poured into 100 ml of water and twice extracted with 100 ml portions of chloroform. The organic layer was dried (magnesium sulfate), concentrated, and azeotroped with toluene under reduced pressure to leave a viscous brown oil which crystallized upon washing with 5% sodium bicarbonate. Recrystallization from ethyl acetate followed by charcoal treatment yielded 23.3 g (31%) of a white crystalline solid, mp 106-107° (lit [4] mp 106-108°).

2-(5-methyl-2-nitrobenzoyl)-1-acetyl-1-methylhydrazine (**IIb**).

Following the same procedure as for **IIa**, 61.6 g (0.34 mole) of 5-methyl-2-nitrobenzoic acid gave 42.6 g (50%) of white crystals after recrystallization from a mixture of ethyl acetate and ethanol, mp 147-149°; nmr (DMSO-d_6): 2.1 (s, 3H, $COCH_3$), 2.57 (s, 3H, Ar-CH_3), 3.2 (s, 3H, NCH_3), 7.6-8.4 (m, 3H, ArH), 11.0 (s, 1H, CONH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.21; H, 5.22; N, 16.69.

Ethyl *N*-Dialkylaminoglycinates **IIIc-e**.

The preparation of ethyl *N*-(4-morpholino)glycinate, **IIIe**, is representative of the general procedure.

A yellow solution containing 14.8 g (0.2 mole) of glyoxylic acid in 20 ml of water was titrated with 2*N* sodium hydroxide to a pink end point (phenolphthalein indicator). The solution was suspended in 200 ml of acetonitrile, 20.4 g (0.2 mole) of *N*-aminomorpholine was added and the mixture was stirred at room temperature for 30 minutes. Sodium cyanoborohydride (12.6 g, 0.2 mole) was added and after 15 minutes of additional stirring glacial acetic acid was introduced dropwise until the solution tested neutral on wet litmus. Stirring was continued for 2 hours, glacial acetic acid being added occasionally to maintain neutral *p*H. Acetonitrile was removed under reduced pressure and the aqueous residue was ice-cooled, adjusted to *p*H 2 with 6*N* hydrochloric acid, concentrated *in vacuo* and azeotroped several times with absolute ethanol. Ethanolic hydrogen chloride (200 ml) was added to the residual slurry and the suspension was refluxed overnight under nitrogen. The inorganic precipitate was filtered and washed with hot ethanol. The combined filtrates were concentrated, adjusted to *p*H 8 with 5% sodium bicarbonate and extracted with ether over 48 hours using a liquid-liquid extractor. The ether extract was dried (magnesium sulfate), concentrated and the residue vacuum distilled. A hydrochloride salt was prepared by precipitation from ethereal hydrogen chloride and recrystallized from an ethanol/ethyl acetate mixture to obtain 18.0 g (40%) of white flakes, mp 135-136°; nmr of free base (deuteriochloroform): 1.3 (t, 3H, CH_3), 2.6-2.9

(m, 5H, $N(CH_2)_2$ and NH, deuterium oxide exchangeable), 3.5-3.9 (m, 6H, NCH_2CO and $O(CH_2)_2$), 4.23 (q, 2H, OCH_2).

Anal. Calcd. for $C_8H_{17}ClN_2O_3$: C, 42.77; H, 7.63; N, 12.47. Found: C, 42.58; H, 7.78; N, 12.47.

Ethyl *N*-(1-Piperidino)glycinate (**IIId**).

The hydrochloride salt was prepared as above and recrystallized from a mixture of ethanol and ethyl acetate to obtain a 31% yield of white needles, mp 123-125°; nmr of free base (deuteriochloroform): 1.3 (t, 3H, CH_3), 1.5-1.9 (m, 6H, $(CH_2)_3$), 2.5-2.9 (m, 5H, $N(CH_2)_2$ and NH, deuterium oxide exchangeable), 3.3 (s, 2H, NCH_2CO), 4.3 (q, 2H, OCH_2).

Anal. Calcd. for $C_9H_{19}ClN_2O_2$: C, 48.54; H, 8.60; N, 12.58. Found: C, 48.65; H, 8.83; N, 12.66.

Ethyl *N*-Dimethylaminoglycinate (**IIIc**).

Aqueous glyoxylic acid (50%, w/w) was used in the same method as described for **IIIe**. The hydrochloride salt was recrystallized from an absolute alcohol/ether mixture to afford 49% of a yellowish crystalline solid, mp 71-73°; nmr of free base (deuteriochloroform): 1.33 (t, 3H, CH_3), 2.5 (s, 6H, $N(CH_3)_2$), 2.8 (s, 1H, NH, deuterium oxide exchangeable), 3.63 (s, 2H, NCH_2CO), 4.3 (q, 2H, OCH_2).

Anal. Calcd. for $C_6H_{15}ClN_2O_2$: C, 39.46; H, 8.28; N, 15.34. Found: C, 39.34; H, 8.55; N, 15.25.

Ethyl *N*-(*o*-Nitrobenzoyl)-*N*-aminoglycinates **IVa-g**. Method A.

To a suspension containing 1.95 g (0.0812 mole) of sodium hydride (57% oil dispersion) in 90 ml of DMF was added 16.7 g (0.0706 mole) of **IIa**. The slurry was stirred for 5 minutes and 13.6 g (0.0812 mole) of ethyl bromoacetate was introduced dropwise at 0-5°. The reaction mixture was stirred at room temperature for 18 hours, poured into water, and extracted with chloroform. After drying (magnesium sulfate) the solution was concentrated *in vacuo* to a brownish oil which crystallized upon washing with ether. Recrystallization from an ethyl acetate/hexane mixture gave 14.8 g (65%) of **IVa** as a white powder, mp 109-111°; nmr (deuteriochloroform): δ 1.1-1.5 (m, 3H, CH_3), 2.37 (s, 3H, $COCH_3$), 3.2 and 3.37 (two s, 3H, NCH_3), 4.2-4.5 (m, 4H, NCH_2CO and OCH_2), 7.6-8.4 (m, 4H, ArH).

Anal. Calcd. for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00. Found: C, 52.05; H, 5.45; N, 13.04.

Using the same procedure as for **IVa**, 37.3 g (0.149 mole) of **IIb** yielded 33.6 g (67%) of **IVb** in the form of a yellowish powder after recrystallization from ethanol, mp 90-92°; nmr (deuteriochloroform): δ 1.1-1.5 (t, 3H, CH_3), 2.37 (s, 3H, $COCH_3$), 2.53 (s, 3H, Ar-CH_3), 3.23 and 3.4 (two s, 3H, NCH_3), 4.1-4.6 (m, 4H, NCH_2CO and OCH_2), 7.5-8.4 (m, 3H, ArH).

Anal. Calcd. for $C_{15}H_{19}N_3O_6$: C, 53.41; H, 5.68; N, 12.46. Found: C, 53.17; H, 5.72; N, 12.44.

Method B. Compounds **IVc-g**.

The preparation of **IVe** is representative of this method, except for **IVd,f**, and **g**, which were done in 2:1 benzene/pyridine solvent. The use of this solvent mixture reduced reaction temperature to 80° and reaction time to 1 hour. The physical properties and analysis are summarized in Table I.

Ethyl *N*-(*o*-Nitrobenzoyl)-*N*-(4-morpholino)glycinate (**IVe**).

A mixture consisting of 3.11 g (0.0186 mole) of *o*-nitrobenzoic acid and 13.5 ml (0.186 mole) of thionyl chloride was refluxed for 5 hours. Excess thionyl chloride was removed by distillation and the residue was suspended in 15 ml of dry pyridine. Next, 3.5 g (0.0186 mole) of **IIIe** was added dropwise at 0° with stirring. The reaction mixture was refluxed for 5 hours, cooled and adjusted to *p*H 8 with 5% sodium bicarbonate. The product was extracted into dichloromethane, dried (magnesium sulfate), concentrated *in vacuo*, and azeotroped with toluene. Recrystallization of the residue afforded yellowish crystals; nmr (deuteriochloroform): δ 1.33 (t, 3H, CH_3), 2.6-2.9 (m, 4H, $N(CH_2)_2$), 3-3.8 (m, 4H, $O(CH_2)_2$), 4.15-4.55 (m, 4H, NCH_2CO and OCH_2), 7.4-8.4 (m, 4H, ArH).

Ethyl *N*-(5-Methyl-2-nitrobenzoyl)-*N*-dimethylaminoglycinate (**IVc**).

This compound had nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_3), 2.4 (s, 6H, $N(CH_3)_2$), 2.5 (s, 3H, Ar-CH_3), 4.2-4.6 (m, 4H, NCH_2CO and OCH_2), 7.4-8.3 (m, 3H, ArH).

Ethyl *N*-(*o*-Aminobenzoyl)-*N*-(1-piperidino)glycinate (**IVd**).

This compound had nmr (deuteriochloroform): δ 1.1-1.8 (m, 9H, CH_3 and $(CH_2)_3$), 2.2-3.3 (m, 4H, $N(CH_2)_2$), 4.1-4.5 (m, 6H, NCH_2CO, OCH_2, and Ar-NH_2, deuterium oxide exchangeable), 6.5-7.4 (m, 4H, ArH).

Ethyl *N*-(5-Methyl-2-nitrobenzoyl)-*N*-(4-morpholino)glycinate (**IVf**).

This compound had nmr (deuteriochloroform): δ 1.33 (t, 3H, CH_3), 2.5 (s, 3H, Ar-CH_3), 2.6-2.9 (m, 4H, $N(CH_2)_2$), 3-3.8 (m, 4H, $O(CH_2)_2$), 4.2-4.5 (m, 4H, NCH_2CO and OCH_2), 7.3-8.2 (m, 3H, ArH).

Ethyl *N*-(5-Chloro-2-nitrobenzoyl)-*N*-(4-morpholino)glycinate (**IVg**).

This compound had nmr (deuteriochloroform): δ 1.33 (t, 3H, CH_3), 2.6-2.9 (m, 4H, $N(CH_2)_2$), 3-3.8 (m, 4H, $O(CH_2)_2$), 4.13-4.5 (m, 4H, NCH_2CO and OCH_2), 7.4-8.2 (m, 3H, ArH).

4-Amino-1,4-benzodiazepine-2,5-diones **VIa-g**.

The preparation of **VIe** is representative of the general procedure. The physical properties and analyses of the compounds are summarized in Table II.

4-(4-Morpholino)-1,4-benzodiazepine-2,5-dione (**VIe**).

A solution containing 3.5 g (0.01 mole) of **IVe** in 100 ml of ethanol was introduced into a hydrogenation flask followed by 0.6 g of 5% Pd/C catalyst. The mixture was hydrogenated on a Parr pressure reaction apparatus at an initial pressure of 50 psi. After 15 minutes the theoretical amount of hydrogen (2.5 lbs) was consumed. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adjusted to *p*H 2 with ethanolic hydrogen chloride and solvent was evaporated. The amine hydrochloride thus obtained was dissolved in 65 ml of dry pyridine and refluxed overnight under nitrogen. Pyridine was distilled off *in vacuo* and the residue was azeotroped with toluene leaving a solid which was recrystallized to obtain a white powder; nmr (DMSO-d_6): δ 3.17-3.5 (m, 4H, $N(CH_2)_2$), 3.8-4 (m, 4H, $O(CH_2)_2$), 4.1 (s, 2H, NCH_2CO), 7.1-8.1 (m, 4H, ArH), 10.4 (s, 1H, CONH, deuterium oxide exchangeable).

4-(*N*-Methylacetamido)-1,4-benzodiazepine-2,5-dione (**VIa**).

This compound had nmr (deuteriochloroform): δ 2.1 and 2.2 (two s, 3H, $COCH_3$), 3.3 and 3.47 (two s, 3H, NCH_3), 4.3 (s, 2H, NCH_2CO), 7.1-8.2 (m, 4H, ArH), 9.2-9.5 (broad s, 1H, CONH, deuterium oxide exchangeable).

7-Methyl-4-(*N*-methylacetamido)-1,4-benzodiazepine-2,5-dione (**VIb**).

This compound had nmr (deuteriochloroform): δ 2.13 and 2.27 (two s, 3H, $COCH_3$), 2.47 (s, 3H, Ar-CH_3), 3.3 and 3.5 (two s, 3H, NCH_3), 4.33 (s, 2H, NCH_2CO), 7.1-8.0 (m, 3H, ArH), 9.5-9.7 (broad s, 1H, CONH, deuterium oxide exchangeable).

7-Methyl-4-dimethylamino-1,4-benzodiazepine-2,5-dione (**VIc**).

This compound had nmr (DMSO-d_6): δ 2.4 (s, 3H, Ar-CH_3), 2.77 (s, 6H, $N(CH_3)_2$), 4.0 (s, 2H, NCH_2CO), 7.1-7.3 (m, 3H, ArH), 10.6 (s, 1H, CONH, deuterium oxide exchangeable).

4-(1-Piperidino)-1,4-benzodiazepine-2,5-dione (**VId**).

This compound had nmr (DMSO-d_6): δ 1.1-2.0 (m, 6H, $(CH_2)_3$), 2.9-3.9 (m, 4H, $N(CH_2)_2$), 3.97 (s, 2H, NCH_2CO), 7.1-8.0 (m, 4H, ArH), 10.55 (s, 1H, CONH, deuterium oxide exchangeable).

7-Methyl-4-(4-morpholino)-1,4-benzodiazepine-2,5-dione (**VIf**).

This compound had nmr (DMSO-d_6): δ 2.35 (s, 3H, Ar-CH_3), 3.0-3.3 (m, 4H, $N(CH_2)_2$), 3.5-3.9 (m, 4H, $O(CH_2)_2$), 4.0 (s, 2H, NCH_2CO), 7.0-7.7 (m, 3H, ArH), 10.4 (s, 1H, CONH, deuterium oxide exchangeable).

7-Chloro-4-(4-morpholino)-1,4-benzodiazepine-2,5-dione (**VIg**).

This compound had nmr (DMSO-d_6): δ 3.0-3.3 (m, 4H, $N(CH_2)_2$), 3.6-3.9 (m, 4H, $O(CH_2)_2$), 4.1 (s, 2H, NCH_2CO), 7.2-7.9 (m, 3H, ArH), 10.7 (s, 1H, CONH, deuterium oxide exchangeable).

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