

Synthesis of Some Substituted Dibenzodiazepinones and Pyridobenzodiazepinones

Victor I. Cohen*, Biyun Jin, Emil I. Cohen and Barry R. Zeeberg

Section of Radiopharmaceutical Chemistry, George Washington University Medical Center,
Washington, DC 20037

Richard C. Reba

Department of Radiology, Nuclear Medicine Section, University of Chicago Hospital,
5841 South Maryland Avenue, Chicago, IL 60637

Received December 19, 1997

Revised March 16, 1998

Some fluoro- and iodo-derivative of 5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one and 11-[[4-[(dialkylamino)butyl]-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones **6** (Scheme 1) and their analogues were synthesized. The synthesis of dibenzodiazepinones **1** (Scheme 1) is based on the reaction between 1,4-phenylenediamine and substituted benzoic acids. The intermediate pyridobenzodiazepinones **3** (Scheme 1) were prepared by condensation of 2-chloro-3-aminopyridine with methyl anthranilate and its chlorine derivative. The condensation of 4-[(halo)alkyl]phenylacetyl chloride with dibenzodiazepinones and pyridobenzodiazepinones followed by the reaction of mono- or dialkyl- or dialkenylamine provides **6** (Scheme 1).

J. Heterocyclic Chem., **35**, 675 (1998).

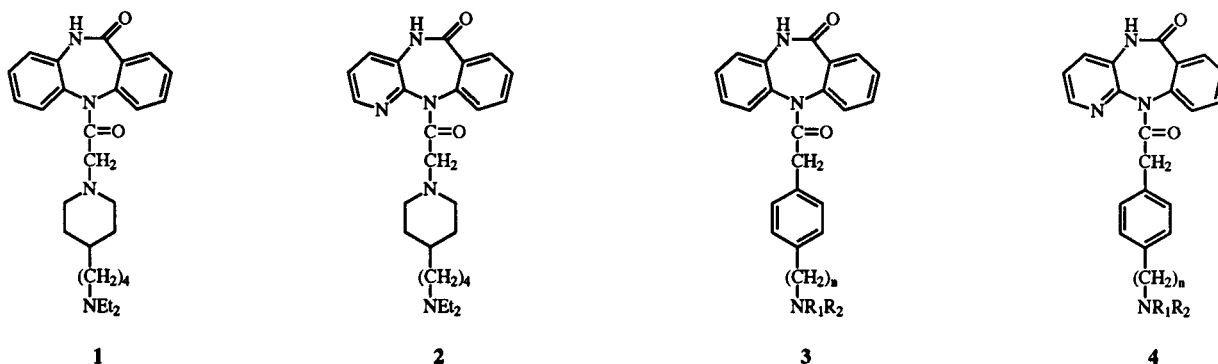
Alzheimer's disease is a neurodegenerative disorder characterized by a profound and specific loss of N. basalis neurons [1,2]. These cholinergic neurons project to the cortex and the degeneration of their presynaptic elements causes the severe cholinergic hypofunction that is characteristic of this disease [3,4]. Much recent evidence suggests that these degenerating presynaptic elements also possess m2 muscarinic autoreceptors: losses in m2 receptors from Alzheimer's disease brain have now been published [5,6].

In our current work, we have focused on developing an m2-selective radioligand. On the basis of existing structure-activity relationships, we have designed and synthesized a m2-selective mAChR antagonist, 5-[[4-[(4-diethylamino)butyl]-1-piperidiny]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (**1**) (Chart 1) [7]. This

compound has been determined to be 10 times more potent at the m2 receptor than the previously reported most highly m2 selective antagonist 11-[[4-[4-(diethylamino)butyl]-1-piperidiny]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**2**) (Chart 1) [7]. However, **1** (Chart 1) did not appear to be able to cross the blood brain barrier. More recently, we have synthesized a series of m2 selective antagonists **3** (Chart 1), capable of crossing the blood brain barrier [8]. The most highly m2 selective compound in this series in *in vitro* studies was found to be 5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (**3**) (Chart 1, R₁ = R₂ = isobutyl; n = 4).

We have therefore prepared some fluoro-, chloro-, and iodo-derivatives of 5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]-

Chart 1



diazepin-11-one (Schemes 1 and 2; Tables 5 and 6) and its tritiated derivative **6** ($R_1 = R_2 = \text{isobutyl}$). We have also prepared compounds with reduced lipophilicity, the derivatives of 11-[[4-[4-(dialkylamino)butyl]-1-phenyl]-acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones (Chart 1, **4**; Scheme 1, **6**, $Y = N$).

Chemistry.

The required 11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*]-[1,4]diazepine and its substituted monofluoro- or mononitro-derivatives (Scheme 1, **1**; Tables 1 and 2, **1a-f**) were prepared from the reaction between fluoro- or nitro-derivative of 2-chlorobenzoic acid and *o*-phenylenediamine by

the modification of method reported by Giani *et al.* [9]. The 2- and 4-nitro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepines (Scheme 1, **1**; Tables 1 and 2, **1e,f**) were converted into the corresponding 2- and 4-amino-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepines (Scheme 1, **1g,h**; Tables 1 and 2) by catalytic reduction (palladium on activated carbon). Reaction of **1g,h** (Scheme 1; Tables 1 and 2) with benzyl chloroformate by a modification of Holley *et al.* [10] provided 2- or 4-benzoyloxycarbonylamino-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepine (Scheme 1, **2**; Tables 1 and 2, **2i,j**). The intermediate pyridobenzodiazepinones (Scheme 1, **3**; Tables 1 and 2, **3a,b**) were prepared by

Scheme 1

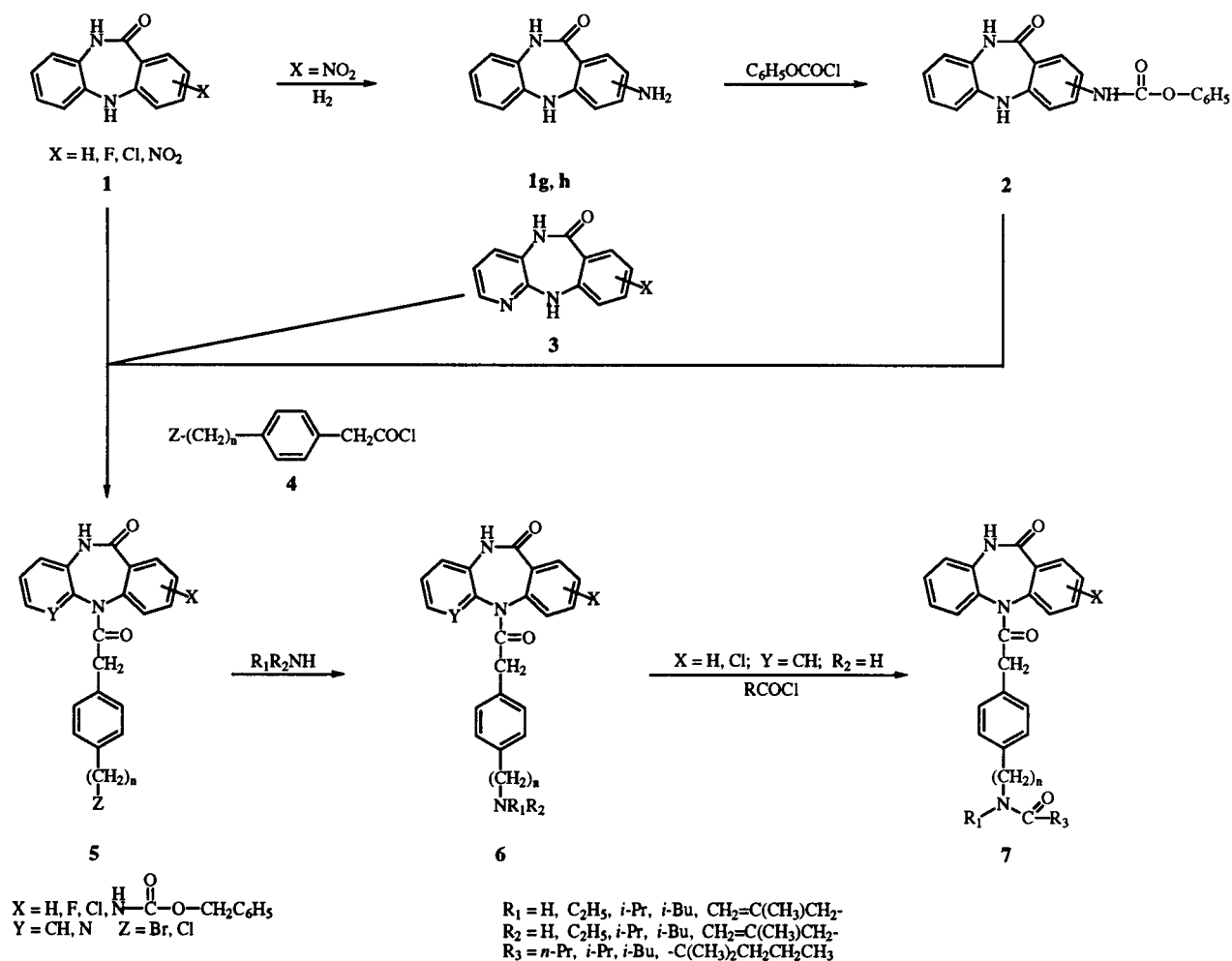
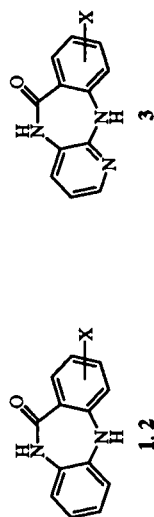


Table 1

Data on 11-Oxo-10,11-dihydro-5*H*-dibenzo[*b-e*][1,4]diazepine, 5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one and their Substitutes 1a-h, 2i,j, 3a,b (Scheme 1, 1-3)

Compound	X	Crystallization and (preparative tlc) solvent	mp °C	Yield (%)	Formula	Solvent	Time (hours)	Temperature
1a	H	1-butanol	228-260	19	C ₁₃ H ₁₀ N ₂ O	ClC ₆ H ₅	24	reflux
1b	1-F	1-butanol	228-229	20	C ₁₃ H ₉ FN ₂ O	ClC ₆ H ₅	24	reflux
1c	3-F	1-butanol	222-229	27	C ₁₃ H ₉ FN ₂ O	ClC ₆ H ₅	24	reflux
1d	2-Cl	1-butanol	260-261	18	C ₁₃ H ₉ ClN ₂ O	ClC ₆ H ₅	24	reflux
1e	2-NO ₂	1,4-dioxane	>300 dec	41	C ₁₃ H ₉ N ₂ O ₃	BuOCH ₂ CH ₂ OH	5	140-150°
1f	4-NO ₂	1,4-dioxane	>300 dec	35	C ₁₃ H ₉ N ₂ O ₃	BuOCH ₂ CH ₂ OH	7	140-150°
1g	2-NH ₂	CHCl ₃ -methanol (10:1)	206-209	92	C ₁₃ H ₁₁ N ₃ O	methanol	48	room temperature
1h	4-NH ₂	CHCl ₃ -methanol (10:1)	210-212	88	C ₁₃ H ₁₁ N ₃ O	methanol	48	room temperature
2i	2-NH-CO-O-CH ₂ C ₆ H ₅	CHCl ₃ -methanol (10:1)	180-182	65	C ₂₁ H ₁₇ N ₃ O ₃	see experimental protocol		
2j	4-NH-CO-O-CH ₂ C ₆ H ₅	CHCl ₃ -methanol (10:1)	197-200	70	C ₂₁ H ₁₇ N ₃ O ₃	see experimental protocol		
3a	H	dimethylformamide	265-270 dec	28	C ₁₂ H ₉ N ₃ O	1,2,4-Cl ₃ C ₆ H ₃	24	115°
3b	2-Cl	dimethylformamide	270 sublimes	72	C ₁₂ H ₈ ClN ₃ O	1,2,4-Cl ₃ C ₆ H ₃	2	160°

Table 2

¹H NMR Data on 11-Oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepine,
5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one and Derivatives 1b-h, 2i-j, 3a,b (Scheme 1, 1-3)

Compound	¹ H NMR: δ [a]	Formula	Elemental Analysis			
			Calcd./Found			
			C	H	F	N
1b	10.07 (1H, br), 7.94 (1H, br), 7.29 (1H, m), 6.99 (4H, m), 6.87 (1H, d, J = 8.2 Hz), 6.74 (1H, dd, J = 10.5, 8.3 Hz)	C ₁₃ H ₉ FN ₂ O	68.42	3.97	8.32	12.27
			68.84	3.72	7.91	11.90
1c	9.87 (1H, br), 8.09 (1H, br), 7.74 (1H, dd, J = 8.8, 7.0 Hz), 6.92 (4H, m), 6.78 (1H, dd, J = 10.7, 2.5 Hz), 6.70 (1H, m)	C ₁₃ H ₉ FN ₂ O	68.42	3.97	8.32	12.27
			68.05	3.79	8.35	12.05
1d	9.88 (1H, br), 8.03 (1H, br), 7.61 (1H, d, J = 2.7 Hz), 7.36 (1H, dd, J = 8.6, 2.7 Hz), 6.94 (5H, m)					
1e	10.07 (1H, br), 9.04 (1H, br), 8.55 (1H, d, J = 2.8 Hz), 8.10 (1H, dd, J = 9.1, 2.8 Hz), 7.05 (1H, d, J = 9.1 Hz), 6.97 (4H, m)	C ₁₃ H ₉ N ₃ O ₃	61.18	3.55		16.46
			60.85	3.42		16.27
1f	10.38 (1H, br), 8.78 (1H, br), 8.19 (1H, dd, J = 8.1, 1.5 Hz), 8.04 (1H, dd, J = 7.7, 1.5 Hz), 7.12 (1H, t, J = 8.1 Hz), 7.03 (4H, m)	C ₁₃ H ₉ N ₃ O ₃	61.18	3.55		16.46
			61.11	3.44		16.32
1g	9.68 (1H, br), 7.18 (1H, br), 6.88 (5H, m), 6.71 (1H, d, J = 8.4 Hz), 6.59 (1H, dd, J = 8.1, 2.7 Hz), 4.76 (2H, br)	C ₁₃ H ₁₁ N ₃ O	69.32	4.92		18.65
			69.46	5.08		18.37
1h	9.88 (1H, br), 7.10 (1H, m), 6.94 (3H, m), 6.87 (1H, dd, J = 7.5, 1.8 Hz), 6.75 (1H, dd, J = 7.8, 1.8 Hz), (2H, m), 5.24 (2H, br)	C ₁₃ H ₁₁ N ₃ O	69.32	4.92		18.65
			68.76	5.02		18.73
2i	9.89 (1H, br), 9.68 (1H, br), 7.83 (1H, d, J = 2.2 Hz), 7.73 (1H, br), 7.47 (1H, dd, J = 8.5, 2.2 Hz), 7.35 (5H, m), 6.94 (5H, m), 5.13 (2H, s)	C ₂₁ H ₁₇ N ₃ O ₃	70.18	4.77		11.69
			69.50	4.70		11.40
2j	10.03 (1H, br), 9.14 (1H, br), 7.52 (1H, d, J = 7.1 Hz), 7.39 (6H, m), 6.94 (6H, m), 5.16 (2H, s)	C ₂₁ H ₁₇ N ₃ O ₃	70.18	4.77		11.69
			69.89	4.79		11.50
3a	9.90 (1H, br), 8.53 (1H, br), 7.87 (1H, dd, J = 4.8, 1.6 Hz), 7.71 (1H, dd, J = 7.9, 1.6 Hz), 7.32 (2H, m), 7.12 (1H, dd, J = 8.14, 0.9 Hz), 6.91 (2H, m)					
3b	10.03 (1H, br), 8.75 (1H, br), 7.88 (1H, dd, J = 4.8, 1.6 Hz), 7.64 (1H, d, J = 2.7 Hz), 7.40 (1H, dd, J = 8.7, 2.7 Hz), 7.29 (1H, dd, J = 7.8, 1.6 Hz), 7.15 (1H, d, J = 8.7 Hz), 6.95 (1H, dd, J = 7.8, 4.8 Hz)					

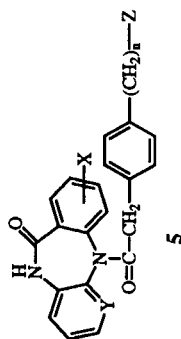
[a] The ¹H nmr spectra were obtained in deuteriochloroform solution.

condensation of 2-chloro-3-aminopyridine with the methyl anthranilate and its chlorine derivative according to the procedure described by Engel *et al.* [11]. The condensation of 4-[(halo)alkyl]phenylacetyl chloride (Scheme 1, 4) with dibenzodiazepinones (Scheme 1, 1,2) and pyridobenzodiazepinones (Scheme 1, 3) will provide compounds 5 (Scheme 1; Tables 3 and 4). The condensa-

tion of mono- or dialkyl- or dialkenylamine with 5 (Scheme 1) provide 5-[[4-[(mono-, dialkyl- or dialkenyl-amino)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones and 11-[[4-[(dialkyl-amino)butyl]-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones, and their derivatives (Scheme 1, 6; Tables 5 and 6). The 2- and 4-benzyl-

Table 3

Data on 5-[4-[(Halo)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzol[*b,e*][1,4]diazepin-11-ones,
11-[4-[(Halo)alkyl]-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and their Derivatives **5a-h** (Scheme 1, 5)



Compound	X	Y	Z	n	Solvent	Flash Chromatography	mp °C	Yield (%)	Formula	Refluxing Solvent	Time (hours)
5a	H	CH	Br	4	CHCl ₃ -methanol (10:1)		70-73	66	C ₂₅ H ₂₂ BrN ₃ O ₂	tetrahydrofuran	5
5b	1-F	CH	Br	4	ethyl acetate-hexane (1:2)		80-82	54	C ₂₅ H ₂₂ FBBrN ₃ O ₂	tetrahydrofuran	4 & room temperature overnight
5c	3-F	CH	Br	4	ethyl acetate-hexane (1:2)		80-83	39	C ₂₅ H ₂₂ FBBrN ₃ O ₂	tetrahydrofuran	4 & room temperature overnight
5d	2-Cl	CH	Cl	3	ethyl acetate-hexane (1:2)		85-90	70	C ₂₄ H ₂₀ Cl ₂ N ₃ O ₂	tetrahydrofuran	5
5e	2-NH-CO-O-CH ₂ C ₆ H ₅	CH	Br	4	CHCl ₃ -methanol (10:1)		99-102	48	C ₃₃ H ₃₀ BrN ₃ O ₄	tetrahydrofuran	room temperature overnight
5f	4-NH-CO-O-CH ₂ C ₆ H ₅	CH	Br	4	ethyl acetate-hexane (1:1)		63-66	38	C ₃₃ H ₃₀ BrN ₃ O ₄	tetrahydrofuran	room temperature overnight
5g	H	N	Br	4	ethyl acetate-hexane (1:1)		97-102	60	C ₂₄ H ₂₂ BrN ₃ O ₂	dioxane	2 & room temperature overnight
5h	8-Cl	N	Br	4	ethyl acetate-hexane (1:1)		75-80	41	C ₂₄ H ₂₁ BrClN ₃ O ₂	dioxane	4

Table 4

¹H NMR Data on 5-[[4-[(Halo)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones, 11-[[4-[(Halo)alkyl]-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and Derivatives **5a-h** (Scheme 1, 5)

Compound	¹ H NMR: δ [a]	Formula	Elemental Analysis Calcd./Found					
			C	H	F	N	Br	Cl
5a	8.81 (1H, br), 7.95 (1H, d, J = 8.1 Hz), 7.61 (1H, t, J = 7.6 Hz), 7.40 (4H, m), 7.23 (1H, m), 7.07 (4H, m), 6.94 (1H, m), 3.64 (2H, s), 3.37 (2H, t, J = 6.7 Hz), 2.53 (2H, m), 1.75 (4H, m)	C ₂₅ H ₂₃ BrN ₂ O ₂	64.80 65.21	5.00 5.11		6.05 6.00	17.24 17.36	
5b	9.09 (1H, br), 7.51 (1H, m), 7.26 (4H, m), 7.06 (5H, m), 6.92 (1H, m), 3.64 (2H, s), 3.50 (2H, m), 2.52 (2H, m), 1.73 (4H, m)	C ₂₅ H ₂₂ BrFN ₂ O ₂	62.38 62.48	4.61 5.09	3.95 3.66	5.82 5.80	16.60 16.33	
5c	9.32 (1H, br), 7.97 (1H, m), 7.13 (10H, m), 3.63 (2H, s), 3.42 (2H, m), 2.51 (2H, m), 1.71 (4H, m)	C ₂₅ H ₂₂ BrFN ₂ O ₂	62.38 62.75	4.61 4.35	3.95 4.15	5.82 6.02	16.60 16.85	
5d	9.06 (1H, br), 7.91 (1H, d, J = 2.2 Hz), 7.55 (1H, dd, J = 8.5, 2.5 Hz), 7.33 (4H, m), 7.00 (5H, m), 3.64 (2H, s), 3.47 (2H, m), 2.65 (2H, m), 2.05 (2H, m)	C ₂₄ H ₂₀ Cl ₂ N ₂ O ₂	65.61 65.12	4.59 4.84		6.38 6.03		
5e	8.86 (1H, br), 8.72 (1H, br), 7.72 (1H, m), 7.34 (8H, m), 7.21 (3H, m), 7.01 (3H, m), 6.93 (1H, m), 5.20 (2H, d, J = 11.0 Hz), 3.61 (2H, d, J = 4.2 Hz), 3.37 (2H, t, J = 6.6 Hz), 2.52 (2H, m), 1.76 (4H, m)	C ₃₃ H ₃₀ BrN ₃ O ₄	64.71 64.68	4.94 5.08		6.86 6.57	13.05 13.04	
5f	8.94 (1H, br), 8.10 (1H, br), 7.68 (1H, dd, J = 7.8, 1.4 Hz), 7.42 (7H, m), 7.29 (2H, m), 7.1 (3H, m), 6.41 (3H, m), 5.23 (2H, d, J = 1.9 Hz), 3.59 (2H, d, J = 2.1 Hz), 3.49 (1H, t, J = 6.2 Hz), 3.36 (1H, t, J = 6.2 Hz), 2.48 (2H, t, J = 7.4 Hz), 1.74 (4H, m)	C ₃₃ H ₃₀ BrN ₃ O ₄	64.71 64.41	4.94 5.26		6.86 6.53	13.05 13.39	
5g	10.11 (1H, br), 8.37 (1H, dd, J = 4.7, 1.7 Hz), 7.95 (1H, d, J = 7.8 Hz), 7.65 (2H, m), 7.43 (2H, m), 7.27 (1H, m), 6.90 (4H, m), 3.83 (2H, s), 3.44 (2H, m), 2.41 (2H, m), 1.63 (4H, m)	C ₂₄ H ₂₂ BrN ₃ O ₂	62.08 62.70	4.78 5.36		9.05 9.39	17.21 17.40	
5h	9.84 (1H, br), 8.38 (1H, dd, J = 4.6, 1.7 Hz), 7.89 (1H, t, J = 1.2 Hz), 7.59 (2H, d, J = 1.7 Hz), 7.32 (2H, m), 6.92 (2H, d, J = 7.6 Hz), 6.82 (2H, d, J = 7.6 Hz), 3.83 (2H, s), 3.47 (2H, t, J = 6.2 Hz), 2.46 (2H, m), 1.66 (4H, m)	C ₂₄ H ₂₁ ClBrN ₃ O ₂	57.79 57.43	4.24 4.38		8.42 8.15	16.01 16.42	7.10 7.45

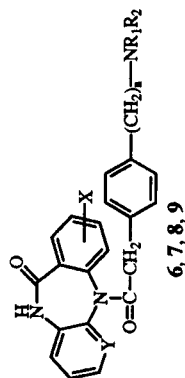
[a] The ¹H nmr spectra were obtained in deuteriochloroform solution.

oxycarbonylamino-5-[[4-[4-(diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones (Scheme 2, **6**; Tables 5 and 6, **6b,c**) were deprotected by hydrogenation at room temperature in the presence of palladium on active carbon according to Fletcher *et al.* [12] to obtain their respective amine (Scheme 2, **8**; Tables 5 and 6, **8b,c**). The 2- and 4-iodo-5-[[4-[4-(diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepine-11-ones (Scheme 2, **9**; Tables 5 and 6, **9b,c**) were synthesized from reaction of

the diazonium intermediate with potassium iodide. Since catalytic reduction of a suitable unsaturated precursor with tritium gas is usually the most satisfactory procedure for tritiating a compound, we have prepared the 5-[[4-[4-[di(2-methylallyl)amino]butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (unsaturated precursor for preparing tritiated 5-[[4-[4-(diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one; Scheme 1, **6** Tables 5 and 6, **6a**).

Table 5

Data on 5-[[4-[(Mono-, dialkyl-, and dialkenylamino)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepin-11-ones, 11-[[4-[(4(Dialkylamino)butyl)-1-phenyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones, and their Derivatives 6a-p, 7a-g, 8b, c, 9b, c (Scheme 1, 6-9)



Compound	X	Y	n	R ₁	R ₂	Solvent (preparative tlc)	Flash Chromatography	Mp (°C)	Yield (%)	Formula	Solvent	Reaction Conditions Reflux (hours)	Room Temperature (hours)
6a	H	CH	4	CH ₂ =C(CH ₃)CH ₂ - <i>i</i> -butyl	CH ₂ =C(CH ₃)CH ₂ - <i>i</i> -butyl	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	47-50	34	C ₃₃ H ₃₇ N ₃ O ₂	CH ₃ CN	16	
6b	2-NH ₂	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	77-80	18	C ₄₁ H ₄₈ N ₄ O ₄	CH ₃ CN	5	16
6c	CO-O-CH ₂ C ₆ H ₅	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	73-77	16	C ₄₁ H ₄₈ N ₄ O ₄	CH ₃ CN	5	16
6d	1-F	CH	4	ethyl	ethyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	48-55	23	C ₂₈ H ₃₂ FN ₃ O ₂	CH ₃ CN	72	
6e	1-F	CH	4	<i>i</i> -propyl	<i>i</i> -propyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	75-81	32	C ₃₁ H ₃₆ FN ₃ O ₂	CH ₃ CN	72	
6f	3-F	CH	4	ethyl	ethyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	57-61	42	C ₂₉ H ₃₂ FN ₃ O ₂	CH ₃ CN	72	
6g	3-F	CH	4	<i>i</i> -propyl	<i>i</i> -propyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	65-72	36	C ₃₁ H ₃₆ FN ₃ O ₂	CH ₃ CN	72	
6h	3-F	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	55-61	28	C ₃₃ H ₄₀ FN ₃ O ₂	CH ₃ CN	72	
6i	2-Cl	CH	3	H	ethyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	76-82	15	C ₂₆ H ₂₆ FN ₃ O ₂	CH ₃ CN	72	
6j	H	CH	4	H	ethyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	62-65	54	C ₂₇ H ₂₉ N ₃ O ₂	CH ₃ CN	48	
6k	H	N	4	ethyl	ethyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	49-56	38	C ₂₈ H ₃₂ N ₄ O ₂	CH ₃ CN	6	
6l	H	N	4	<i>i</i> -propyl	<i>i</i> -propyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	68-75	24	C ₃₀ H ₃₆ N ₄ O ₂	CH ₃ CN	16	
6m	H	N	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	60-69	22	C ₃₂ H ₄₀ N ₄ O ₂	CH ₃ CN	6	
6n	8-Cl	N	4	ethyl	ethyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	60-67	62	C ₂₈ H ₃₁ ClN ₄ O ₂	CH ₃ CN	16	
6o	8-Cl	N	4	<i>i</i> -propyl	<i>i</i> -propyl	methanol-NH ₄ OH, 98:2	methanol-NH ₄ OH, 98:2	68-76	18	C ₃₀ H ₃₅ ClN ₄ O ₂	CH ₃ CN	16	
6p	8-Cl	N	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	64-69	56	C ₃₂ H ₃₉ ClN ₄ O ₂	CH ₃ CN	16	
7a	H	CH	3	ethyl	Pr-C(Me) ₂ -C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	72-75	68	C ₃₃ H ₃₉ N ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
7b	2-Cl	CH	3	ethyl	Pr-C(Me) ₂ -C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	70-79	54	C ₃₃ H ₃₈ ClN ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
7c	H	CH	4	ethyl	Pr-C(Me) ₂ -C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	60-65	62	C ₃₄ H ₄₁ N ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
7d	2-Cl	CH	4	ethyl	Pr-C(Me) ₂ -C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	59-70	42	C ₃₄ H ₄₀ ClN ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
7e	H	CH	4	<i>i</i> -butyl	Pr-C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	57-68	48	C ₃₃ H ₃₉ N ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
7f	H	CH	4	<i>i</i> -butyl	Me ₂ CH-C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	80-88	32	C ₃₃ H ₃₉ N ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
7g	H	CH	4	<i>i</i> -butyl	Me ₂ CH-CH ₂ -C=O	ethyl acetate-hexane, 1:1	ethyl acetate-hexane, 1:1	55-65	28	C ₃₄ H ₄₁ N ₃ O ₃	tetrahydrofuran, PhNMe ₂	1 (dry ice/acetone)	16
8b	2-NH ₂	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	92-98	85	C ₃₃ H ₄₂ N ₄ O ₂	PhNMe ₂	1 (dry ice/acetone)	72
8c	4-NH ₂	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 20:1	CHCl ₃ -methanol, 20:1	150-151	80	C ₃₃ H ₄₂ N ₄ O ₂	ethanol	1 (dry ice/acetone)	72
9b	2-I	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	136-141	15	C ₃₃ H ₄₀ IN ₃ O ₂	ethanol	see experimental protocol	
9c	4-I	CH	4	<i>i</i> -butyl	<i>i</i> -butyl	CHCl ₃ -methanol, 10:1	CHCl ₃ -methanol, 10:1	67-73	12	C ₃₃ H ₄₀ IN ₃ O ₂	see experimental protocol	see experimental protocol	

Table 6

¹H NMR Data on 5-[[4-[(Mono-, dialkyl-, and dialkenylamino)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones, 11-[[4-[4-(Dialkylamino)butyl-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepines and Derivatives 6a-p, 7a-g, 8b,c, 9b,c (Scheme 1, 6-9)

Compound	¹ H NMR: δ [a]	Formula	Elemental Analysis					
			Calcd./Found					
			C	H	F	N	Cl	I
6a	8.49 (1H, br), 7.96 (1H, m), 7.59 (1H, t, J = 7.6 Hz), 7.44 (2H, m), 7.31 (2H, m), 7.22 (1H, m), 7.02 (4H, m), 6.91 (1H, m), 4.86 (2H, s), 4.80 (2H, s), 3.62 (2H, s), 2.80 (4H, s), 2.51 (2H, m), 2.28 (2H, t, J = 7.0 Hz), 1.71 (6H, s), 1.56 (2H, m), 1.43 (2H, m)	C ₃₃ H ₃₇ N ₃ O ₂	78.07	7.35		8.28		
			77.63	7.17		8.16		
6b	8.75 (1H, br), 8.38 (1H, br), 7.73 (1H, m), 7.33 (8H, m), 7.18 (2H, m), 7.02 (4H, m), 6.90 (1H, m), 5.20 (2H, d, J = 9.8 Hz), 3.60 (2H, s), 2.53 (2H, t, J = 7.5 Hz), 2.29 (2H, t, J = 6.9 Hz), 2.01 (4H, d, J = 7.1 Hz), 1.62 (4H, m), 1.41 (2H, m), 0.85 (12H, d, J = 6.5 Hz)	C ₄₁ H ₄₈ N ₄ O ₄	74.52	7.32		8.48		
			73.82	7.35		8.30		
6c	8.65 (1H, br), 8.08 (1H, br), 7.67 (1H, d, J = 7.6 Hz), 7.32 (8H, m), 7.04 (5H, m), 6.85 (2H, d, J = 7.9 Hz), 5.22 (2H, s), 3.58 (2H, d, J = 2.8 Hz), 2.48 (2H, t, J = 7.5 Hz), 2.28 (2H, t, J = 6.9 Hz), 2.01 (4H, d, J = 7.1 Hz), 1.59 (4H, m), 1.39 (2H, m), 0.85 (12H, d, J = 6.5 Hz)	C ₄₁ H ₄₈ N ₄ O ₄	74.52	7.32		8.48		
			74.19	7.22		8.36		
6d	8.61 (1H, br), 7.48 (1H, m), 7.19 (8H, m), 6.92 (2H, m), 3.67 (2H, m), 2.51 (6H, m), 2.41 (2H, m), 1.56 (2H, m), 1.42 (2H, m), 1.00 (6H, t, J = 7.2 Hz)	C ₂₉ H ₃₂ FN ₃ O ₂	73.55	6.81	4.01	8.87		
			73.19	6.49	4.18	8.68		
6e	7.50 (1H, m), 7.25 (4H, m), 7.06 (5H, m), 6.88 (1H, m), 3.63 (2H, m), 2.99 (2H, m), 2.53 (2H, m), 2.37 (2H, m), 1.54 (2H, m), 1.42 (2H, m), 0.98 (12H, d, J = 6.5 Hz)	C ₃₁ H ₃₆ FN ₃ O ₂	74.22	7.23	3.79	8.38		
			73.99	7.23	3.93	8.25		
6f	9.32 (1H, br), 7.96 (1H, m), 7.33 (2H, m), 7.14 (6H, m), 6.91 (2H, m), 3.63 (2H, m), 2.52 (6H, m), 2.38 (2H, m), 1.52 (2H, m), 1.42 (2H, m), 1.00 (6H, t, J = 7.1 Hz)	C ₂₉ H ₃₂ FN ₃ O ₂	73.55	6.81	4.01	8.87		
			73.34	6.93	4.07	8.79		
6g	9.02 (1H, br), 7.97 (1H, m), 7.33 (2H, m), 7.13 (6H, m), 6.91 (2H, m), 3.62 (2H, s), 2.98 (2H, m), 2.51 (2H, m), 2.36 (2H, m), 1.51 (2H, m), 1.39 (2H, m), 0.97 (12H, d, J = 6.5 Hz)	C ₃₁ H ₃₆ FN ₃ O ₂	74.22	7.23	3.79	8.38		
			74.00	7.28	3.81	8.29		
6h	8.54 (1H, br), 7.96 (1H, m), 7.32 (2H, m), 7.23 (2H, m), 7.04 (6H, m), 3.62 (2H, s), 2.52 (2H, m), 2.28 (2H, t, J = 6.8 Hz), 2.01 (4H, d, J = 7.1 Hz), 1.62 (4H, m), 1.41 (2H, m), 0.85 (12H, d, J = 6.5 Hz)	C ₃₃ H ₄₀ FN ₃ O ₂	74.83	7.61	3.59	7.93		
			74.62	7.70	3.67	7.84		
6i	7.90 (1H, d, J = 2.4 Hz), 7.53 (1H, dd, J = 8.5, 2.5 Hz), 7.32 (4H, m), 7.08 (4H, m), 6.85 (1H, m), 3.64 (2H, s), 2.61 (6H, m), 2.18 (1H, s), 1.77 (2H, m), 1.09 (3H, t, J = 7.1 Hz)	C ₂₆ H ₂₆ ClN ₃ O ₂	69.71	5.85		7.91	9.38	
			69.91	6.00		7.53	9.12	
6j	7.91 (1H, m), 7.58 (1H, t, J = 7.5 Hz), 7.42 (3H, m), 7.24 (2H, m), 7.05 (4H, m), 6.78 (1H, d, J = 7.7 Hz), 3.68 (2H, m), 2.62 (6H, m), 2.17 (1H, s), 1.61 (2H, m), 1.46 (2H, m), 1.10 (3H, t, J = 7.1 Hz)	C ₂₇ H ₂₉ N ₃ O ₂	75.85	6.84		9.83		
			75.38	6.74		9.50		
6k	8.36 (1H, t, J = 3.1 Hz), 7.9 (1H, d, J = 7.7 Hz), 7.62 (2H, m), 7.42 (1H, m), 7.26 (2H, m), 6.97 (3H, m), 6.79 (1H, m), 3.84 (2H, m), 2.55 (6H, m), 2.39 (2H, m), 1.53 (2H, m), 1.42 (2H, m), 1.00 (6H, t, J = 7.1 Hz)	C ₂₈ H ₃₂ N ₄ O ₂	73.66	7.06		12.27		
			72.82	7.04		11.88		

(Continued)

Table 6 (cont.)

Compound	¹ H NMR: δ [a]	Formula	Elemental Analysis				
			Calcd./Found				
			C	H	F	N	Cl I
6l	8.37 (1H, m), 7.93 (1H, d, J = 7.9 Hz), 7.63 (2H, m), 7.42 (1H, m), 7.27 (2H, m), 6.96 (2H, m), 6.83 (2H, m), 3.83 (2H, m), 2.98 (2H, m), 2.48 (2H, t, J = 7.4 Hz), 2.36 (2H, t, J = 7.4 Hz), 1.50 (2H, m), 1.39 (2H, m), 0.98 (12H, d, J = 6.5 Hz)	C ₃₀ H ₃₆ N ₄ O ₂	74.35 73.80	7.49 7.40		11.56 11.37	
6m	8.92 (1H, br), 8.38 (1H, dd, J = 4.2, 1.8 Hz), 7.93 (1H, d, J = 7.7 Hz), 7.62 (2H, m), 7.43 (1H, m), 7.28 (2H, m), 6.94 (2H, m), 6.84 (2H, m), 3.81 (2H, s), 2.46 (2H, m), 2.26 (2H, m), 2.00 (4H, d, J = 6.9 Hz), 1.67 (2H, m), 1.52 (2H, m), 1.36 (2H, m), 0.85 (12H, d, J = 6.5 Hz)	C ₃₂ H ₄₀ N ₄ O ₂	74.47 74.67	7.86 7.74		10.93 10.67	
6n	8.36 (1H, m), 7.87 (1H, m), 7.56 (2H, m), 7.24 (2H, m), 6.91 (2H, m), 6.75 (2H, m), 3.86 (2H, m), 2.54 (6H, m), 2.38 (2H, m), 1.52 (2H, m), 1.30 (2H, m), 1.00 (6H, t, J = 7.1 Hz)	C ₂₈ H ₃₁ ClN ₄ O ₂	68.49 68.83	6.36 6.39		11.42 11.12	7.22 7.28
6o	8.38 (1H, t, J = 23.2 Hz), 7.88 (1H, t, J = 1.4 Hz), 7.57 (2H, m), 7.25 (2H, m), 6.94 (2H, d, J = 7.5 Hz), 6.79 (2H, m), 3.82 (2H, s), 2.99 (2H, m), 2.49 (2H, t, J = 7.5 Hz), 2.36 (2H, t, J = 7.2 Hz), 1.50 (2H, m), 1.37 (2H, m), 0.98 (12H, d, J = 6.6 Hz)	C ₃₀ H ₃₅ ClN ₄ O ₂	69.43 69.00	6.80 6.81		10.79 10.53	6.83 6.87
6p	8.77 (1H, br), 8.39 (1H, t, J = 3.2 Hz), 7.86 (1H, s), 7.57 (2H, d, J = 1.7 Hz), 7.28 (2H, m), 6.94 (2H, d, J = 7.4 Hz), 6.81 (2H, m), 3.81 (2H, s), 2.47 (2H, t, J = 7.5 Hz), 2.27 (2H, t, 6.8 Hz), 2.00 (4H, d, J = 7.1 Hz), 1.64 (2H, m), 1.53 (2H, m), 1.37 (2H, m), 0.85 (12H, d, J = 6.5 Hz)	C ₃₂ H ₃₉ ClN ₄ O ₂	70.25 70.11	7.18 7.21		10.24 10.17	6.48 6.48
7a	9.08 (1H, br), 7.87 (1H, m), 7.55 (1H, t, J = 7.2 Hz), 7.26 (7H, m), 6.97 (2H, d, J = 7.7 Hz), 6.68 (1H, m), 3.65 (2H, m), 3.45 (4H, m), 2.59 (2H, m), 1.82 (2H, m), 1.53 (2H, m), 1.24 (11H, m), 0.89 (3H, t, J = 7.1 Hz)	C ₃₃ H ₃₈ N ₃ O ₃	75.40 74.90	7.48 7.43		7.99 7.90	
7b	9.38 (1H, br), 7.83 (1H, s), 7.49 (1H, d, J = 8.4 Hz), 7.38 (2H, d, J = 8.4 Hz), 7.21 (4H, m), 6.96 (2H, d, J = 8.4 Hz), 6.64 (1H, m), 3.72 (2H, m), 3.42 (4H, m), 2.54 (2H, m), 1.89 (2H, m), 1.53 (2H, m), 1.27 (11H, m), 0.89 (3H, t, J = 7.2)	C ₃₃ H ₃₈ ClN ₃ O ₃	70.76 70.79	6.84 6.90		7.50 7.32	6.33 6.59
7c	8.87 (1H, br), 7.90 (1H, m), 7.54 (1H, m), 7.27 (7H, m), 6.98 (2H, m), 6.84 (1H, m), 3.6 (2H, m), 3.37 (2H, m), 3.26 (2H, m), 2.53 (2H, m), 1.50 (6H, m), 1.20 (11H, m), 0.85 (3H, t, J = 7.3 Hz)	C ₃₄ H ₄₁ N ₃ O ₃	75.66 75.72	7.66 7.64		7.79 7.43	
7d	9.04 (1H, br), 7.89 (1H, s), 7.53 (1H, d, J = 8.5 Hz), 7.29 (5H, m), 7.00 (3H, m), 6.82 (1H, m), 3.65 (2H, s), 3.38 (4H, m), 2.56 (2H, m), 1.53 (6H, m), 1.23 (11H, m), 0.88 (3H, t, J = 7.2 Hz)	C ₃₄ H ₄₀ ClN ₃ O ₃	71.13 70.86	7.02 7.04		7.32 7.15	6.17 6.36
7e	8.88 (1H, br), 7.92 (1H, m), 7.57 (1H, m), 7.29 (6H, m), 6.97 (3H, m), 7.78 (1H, m), 6.39 (2H, s), 3.10 (4H, m), 2.55 (2H, m), 2.26 (2H, m), 1.91 (1H, m), 1.62 (6H, m), 0.90 (9H, m)	C ₃₃ H ₃₉ N ₃ O ₃	75.40 74.73	7.48 7.43		7.99 7.85	
7f	8.71 (0.5H, br), 8.50 (0.5H, br), 7.94 (1H, m), 7.58 (1H, m), 7.31 (7H, m), 6.97 (3H, m), 3.63 (2H, s), 3.14 (4H, m), 2.76 (1H, m), 2.56 (2H, m), 1.93 (1H, m), 1.55 (4H, m), 1.10 (6H, dd, J = 6.7, 1.9 Hz), 0.89 (6H, dd, J = 22.5, 6.6 Hz)	C ₃₃ H ₃₉ N ₃ O ₃	75.40 75.56	7.48 7.49		7.99 7.75	

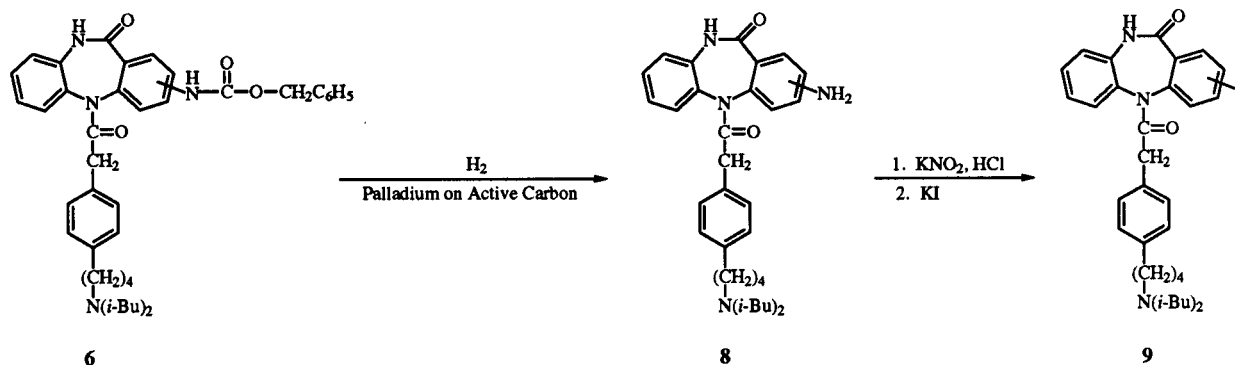
(Continued)

Table 6 (cont.)

Compound	¹ H NMR: δ [a]	Formula	Elemental Analysis Calcd./Found					
			C	H	F	N	Cl	I
7g	8.78 (1H, br), 7.93 (1H, m), 7.58 (1H, m), 7.29 (7H, m), 6.94 (3H, m), 3.63 (2H, m), 3.12 (4H, m), 2.55 (2H, m), 2.17 (2H, m), 1.91 (1H, m), 1.81 (1H, m), 1.54 (4H, m), 0.89 (12H, m)	C ₃₄ H ₄₁ N ₃ O ₃	75.66 75.18	7.66 7.64		7.79 7.52		
8b	8.92 (1H, br), 7.20 (9H, m), 6.90 (1H, m), 6.80 (1H, m), 3.96 (1H, br), 3.83 (1H, br), 3.61 (2H, m), 2.53 (2H, m), 2.29 (2H, m), 2.01 (4H, d, J = 7.1 Hz), 1.63 (4H, m), 1.41 (2H, m), 0.85 (12H, d, J = 6.5 Hz)	C ₃₃ H ₄₂ N ₄ O ₂	75.25 75.46	8.04 8.08		10.64 10.37		
8c	8.33 (1H, br), 7.26 (6H, m), 6.99 (4H, m), 6.89 (1H, d, J = 8.0 Hz), 4.19 (1H, br), 4.01 (1H, br), 3.60 (2H, s), 2.52 (2H, t, J = 7.2 Hz), 2.29 (2H, t, J = 7.1 Hz), 2.01 (4H, d, J = 7.2 Hz), 1.62 (4H, m), 1.41 (2H, m), 0.85 (12H, dd, J = 6.5, 2.6 Hz)	C ₃₃ H ₄₂ N ₄ O ₂	75.25 75.07	8.04 8.01		10.64 10.52		
9b	8.77 (1H, br), 8.25 (1H, s), 7.88 (1H, dd, J = 8.3, 2.1 Hz), 7.31 (2H, m), 7.21 (1H, m), 7.02 (4H, m), 6.89 (2H, m), 3.62 (2H, s), 2.51 (2H, m), 2.27 (2H, m), 2.00 (4H, d, J = 7.1 Hz), 1.63 (4H, m), 1.39 (2H, m), 0.85 (12H, d, J = 6.6 Hz)	C ₃₃ H ₄₀ IN ₃ O ₂	62.16 62.37	6.32 6.31		6.60 6.66	19.90 19.85	
9c	8.40 (0.5H, br), 8.20 (0.5H, br), 8.13 (0.5H, dd, J = 7.9, 1.5 Hz), 8.04 (0.5H, dd, J = 7.9, 1.4 Hz), 7.88 (1H, m), 7.73 (1H, m), 7.25 (2H, m), 7.10 (1H, m), 6.98 (4H, m), 6.85 (1H, m), 3.59 (2H, m), 2.50 (2H, m), 2.27 (2H, m), 1.99 (4H, m), 1.66 (2H, m), 1.54 (2H, m), 1.38 (2H, m), 0.84 (12H, m)	C ₃₃ H ₄₀ IN ₃ O ₂	62.16 62.48	6.32 6.25		6.60 6.80	19.90 19.79	

[a] The ¹H nmr spectra were obtained in deuteriochloroform solution.

Scheme 2



EXPERIMENTAL

The melting points were obtained on a Fisher-John apparatus. The ^1H nmr spectra were recorded on a Bruker AC-300 instrument and expressed as parts per million (δ) from internal tetramethylsilane. The hplc was performed on an Altex Model 110A. 2-Chlorobenzoic acid, *o*-phenylenediamine, 2-aminobenzoic acid, 3-amino-2-chloropyridine, 2,5-dichlorobenzoic acid, 2-chloro-4-fluorobenzoic acid, 2-chloro-6-fluorobenzoic acid, 2-chloro-3-nitrobenzoic acid, 2-chloro-5-nitrobenzoic acid, benzyl chloroformate, palladium on activated carbon, mono- and dialkylamines, and chloroacetyl chloride were obtained from Aldrich.

11-Oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepine and its Fluoro-, Chloro- and Nitro-derivatives (Scheme 1, 1; Tables 1 and 2, 1a-f).

They were prepared by condensation of *o*-phenylenediamine with 2-chlorobenzoic acid or its derivatives by the modification of the method reported by Giani *et al.* [9].

5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one and its 8-Chloro-derivative (Scheme 1, 3; Tables 1 and 2, 3a,b).

They were prepared by treating methyl 2-aminobenzoate or methyl 2-amino-5-chlorobenzoate with 2-chloro-3-aminopyridine by the procedure described by Engel *et al.* [11].

Procedure for the Preparation of 2- and 4-Amino-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepines (Scheme 1, 1g,h; Tables 1 and 2).

A mixture of 0.77 g (3 mmoles) of 2- or 4- nitro-derivative (Scheme 1, 1; Table 1, 1e,f), 300 ml of methanol and 0.2 g Pd-C 10% was shaken with hydrogen in a Parr pressure flask at 3 atmospheres and room temperature for 48 hours. The catalyst was filtered and the solvent was evaporated under reduced pressure. The residue purified by preparative tlc using chloroform/methanol (10:1) as eluent.

Procedure for the Preparation of 2- and 4-Benzyloxycarbonyl-amino-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepines (Scheme 1, 2; Tables 1 and 2, 2i,j).

They were prepared by treating a solution of 0.7 g (3.11 mmoles) 2- or 4-amino-derivative (Scheme 1, 1g,h; Table 1), and 0.467 ml of triethylamine in 10 ml of tetrahydrofuran and cooled in ice bath with 0.531 g (0.45 ml) of benzyl chloroformate. After 10 minutes the mixture was removed from the ice-bath and left at room temperature for 30 minutes with stirring. The mixture was poured into water, made basic with sodium bicarbonate solution, and extracted with chloroform. The extract was washed with water, dried, and purified by preparative tlc using chloroform/methanol (10:1) as eluent.

General Procedure for the Preparation of 5-[[4-[(Halo)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones, 11-[[4-[(Halo)alkyl]-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and their Derivatives (Scheme 1, 5; Tables 3 and 4, 5a-h).

To 0.05 mole of 4-[(halo)alkyl]phenylacetic acid in 100 ml of chloroform, was added thionyl chloride (30 ml), and it was heated at reflux for 3 hours. The solvent and the excess thionyl

chloride were evaporated under reduced pressure. To the residue was added 1, 2 or 3 (Scheme 1) 0.05 mole of *N,N*-dimethylaniline (3 ml), and tetrahydrofuran or dioxane (100 ml), and refluxed for 2-5 hours or at room temperature (Table 3). The mixture was evaporated to dryness under reduced pressure. A 10% potassium bicarbonate solution was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. Purification by flash chromatography on silica gel, provided the product.

General Procedure for the Preparation of 5-[[4-[(Mono-, Dialkyl- and Dialkenylamino)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones, 11-[[4-[(Dialkylamino)butyl]-1-phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and their Derivatives (Scheme 1, 6; Tables 5 and 6, 6a-p).

A solution of 5 (5 mmoles), mono- or dialkyl or dialkenylamine (3 ml), and sodium carbonate (3 g), in acetonitrile (40 ml), were refluxed (Table 5). The solvent was removed under reduced pressure and the residue was partitioned between chloroform-water. The organic layer was separated, washed with water, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Procedure for the Preparation of 5-[[4-[(Monoalkylmonoacylamino)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones and their Derivatives (Scheme 1, 7; Tables 5 and 6, 7a-g).

A solution of monoalkylamine derivative 6 (2 mmoles) and *N,N*-dimethylaniline (1.5 g) in tetrahydrofuran (30 ml) was cooled in a dry ice/acetone bath, and treated with acyl chloride (4 ml). The mixture was stirred overnight at room temperature, and then washed with 5% potassium carbonate and water. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography or preparative tlc.

General Procedure for the Preparation of 2- and 4-Amino-5-[[4-[(diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones (Scheme 2, 8; Tables 5 and 6, 8b,c).

A solution of the benzyloxycarbonyl derivative 6b or 6c (1.32 g, 2 mmoles) in ethanol (200 ml) was hydrogenated over 10% Pd-C (0.5 g) in a Parr pressure flask at 3 atmosphere and room temperature for 72 hours. The catalyst was filtered and the solvent was removed under reduced pressure. The residue was purified first with flash column chromatography and then, if necessary, by preparative tlc, to obtain the respective amino-derivative (Scheme 2, 8; Tables 5 and 6, 8b,c).

General Procedure for the Preparation of 2- and 4-Iodo-5-[[4-[(diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-ones (Scheme 2, 9; Tables 5 and 6, 9b,c).

A solution of 8b or 8c (0.53 g, 1 mmole) in 15 ml of 10% hydrochloric acid and 3 ml of acetone was cooled to 0° followed by treatment with a solution of sodium nitrite (90 mg, 1.3 mmoles) in 2 ml of water. A yellow suspension formed as the solution was stirred for 15 minutes at 0°, and then urea (100 mg) was added. To the suspension of diazonium derivative was added a

solution of potassium iodide (200 mg, 1.2 mmoles) in 5 ml of water slowly and with stirring. The mixture was allowed to stand overnight at room temperature with stirring, then made alkaline by the addition of 10% solution of sodium hydroxide and finally was extracted with chloroform. The organic layer was washed with water and dried over magnesium sulfate. Rotary evaporation of the solvent afforded the crude product. Preparative tlc using chloroform-methanol (10:1) as eluent provides the pure compound.

Procedure for the Preparation of Tritiated 5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one.

Tritiation of 5-[[4-[(4-di(2-methylallyl)amino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one (Tables 5 and 6, 6a), was performed by Dupont as follows. To a solution of 61.6 mg of 6a in 2 ml of ethanol was added 75 mg of 5% Pd/C and 80 Ci of tritium gas. The mixture was stirred for 2 hours at room temperature. An uptake of 6.5 ml of tritium was observed.

The labile material was removed with ethanol. Purification of [3H]5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one was first carried out by preparative tlc using chloroform/methanol (20:1) as the eluent followed by hplc using RP C₁₈ Radial Pak Cartridge in a Z-Module and methanol/0.01 M phosphate buffer pH 7.4 (1:9) as the eluent. The fraction eluting at 10 minutes was collected; tlc [silica gel, chloroform/methanol (20:1)] R_f 0.50. The R_f values of co-spotted [3H]5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one and 5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one are identical.

Acknowledgments.

This work was supported in part by Grants NS22215 from the National Institutes of Health, DHEW, and DE FG05 93ER61588 from the Department of Energy.

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