# Synthesis of Some Substituted Dibenzodiazepinones and Pyridobenzodiazepinones



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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).

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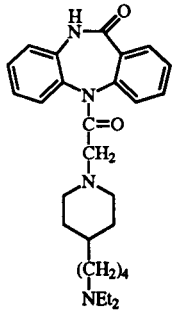
Alzheimer's disease is a neurodegenerative disorder characterized by a profound and specific loss of N. basalis neurons [1,2]. These cholinergic neurons project to the cortex and the degeneration of their presynaptic elements causes the severe cholinergic hypofunction that is characteristic of this disease [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].

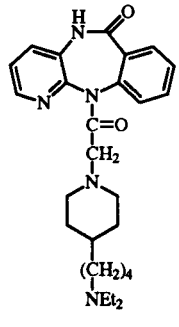
In our current work, we have focused on developing an m2-selective radioligand. On the basis of existing structure-activity relationships, we have designed and synthesized a m2-selective mAChR antagonist, 5-[[4-[(4-diethylamino)butyl]-1-piperidinyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (**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-piperidinyl]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, $R_1 = R_2$ = 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]-

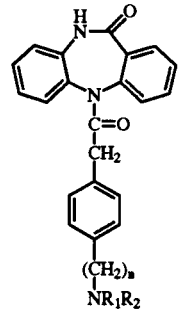
Chart 1



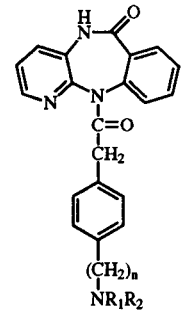
**1**



**2**



**3**



**4**

diazepin-11-one (Schemes 1 and 2; Tables 5 and 6) and its tritiated derivative **6** ($R_1$ = $R_2$ = 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-benzyloxycarbonylamino-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

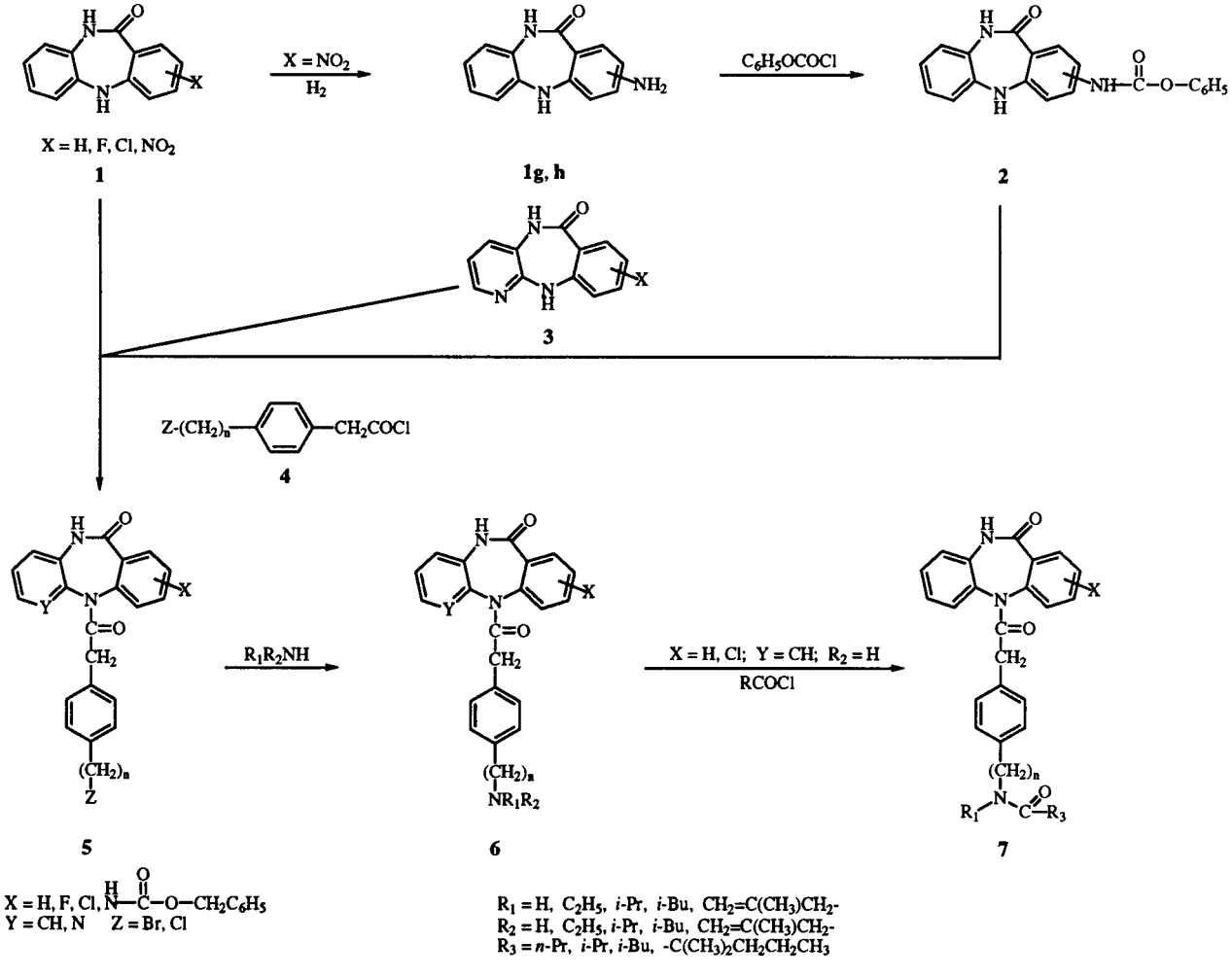
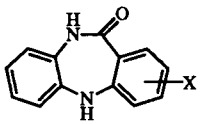
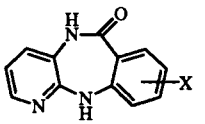


Table 1

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**)



**1, 2**



**3**

| Compound | X | Crystallization and (preparative tlc) solvent | mp °C | Yield (%) | Formula | Solvent | Time (hours) | Temperature |
|---|---|---|---|---|---|---|---|---|
| **1a** | H | 1-butanol | 228-260 | 19 | $C_{13}H_{10}N_2O$ | $ClC_6H_5$ | 24 | reflux |
| **1b** | 1-F | 1-butanol | 228-229 | 20 | $C_{13}H_9FN_2O$ | $ClC_6H_5$ | 24 | reflux |
| **1c** | 3-F | 1-butanol | 222-229 | 27 | $C_{13}H_9FN_2O$ | $ClC_6H_5$ | 24 | reflux |
| **1d** | 2-Cl | 1-butanol | 260-261 | 18 | $C_{13}H_9ClN_2O$ | $ClC_6H_5$ | 24 | reflux |
| **1e** | 2-$NO_2$ | 1,4-dioxane | >300 dec | 41 | $C_{13}H_9N_3O_3$ | $BuOCH_2CH_2OH$ | 5 | 140-150° |
| **1f** | 4-$NO_2$ | 1,4-dioxane | >300 dec | 35 | $C_{13}H_9N_3O_3$ | $BuOCH_2CH_2OH$ | 7 | 140-150 ° |
| **1g** | 2-$NH_2$ | $CHCl_3$-methanol (10:1) | 206-209 | 92 | $C_{13}H_{11}N_3O$ | methanol | 48 | room temperature |
| **1h** | 4-$NH_2$ | $CHCl_3$-methanol (10:1) | 210-212 | 88 | $C_{13}H_{11}N_3O$ | methanol | 48 | room temperature |
| **2i** | 2-NH-CO-O-$CH_2C_6H_5$ | $CHCl_3$-methanol (10:1) | 180-182 | 65 | $C_{21}H_{17}N_3O_3$ | see experimental protocol | | |
| **2j** | 4-NH-CO-O-$CH_2C_6H_5$ | $CHCl_3$-methanol (10:1) | 197-200 | 70 | $C_{21}H_{17}N_3O_3$ | see experimental protocol | | |
| **3a** | H | dimethylformamide | 265-270 dec | 28 | $C_{12}H_9N_3O$ | 1,2,4-$Cl_3C_6H_3$ | 24 | 115° |
| **3b** | 2-Cl | dimethylformamide | 270 sublimes | 72 | $C_{12}H_8ClN_3O$ | 1,2,4-$Cl_3C_6H_3$ | 2 | 160° |

Table 2

$^1$H 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)

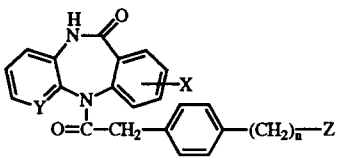
| Compound | $^1$H NMR: δ [a] | Formula | Elemental Analysis Calcd./Found | | | |
|---|---|---|---|---|---|---|
| | | | C | H | F | N |
| **1b** | 10.07 (1H, br), 7.94 (1H, br), 7.29 (1H, m), 6.99 (4H, m), 6.87 (1H, d, J = 8.2 Hz), 6.74 (1H, dd, J = 10.5, 8.3 Hz) | $C_{13}H_9FN_2O$ | 68.42<br>68.84 | 3.97<br>3.72 | 8.32<br>7.91 | 12.27<br>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) | $C_{13}H_9FN_2O$ | 68.42<br>68.05 | 3.97<br>3.79 | 8.32<br>8.35 | 12.27<br>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) | $C_{13}H_9N_3O_3$ | 61.18<br>60.85 | 3.55<br>3.42 | | 16.46<br>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) | $C_{13}H_9N_3O_3$ | 61.18<br>61.11 | 3.55<br>3.44 | | 16.46<br>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) | $C_{13}H_{11}N_3O$ | 69.32<br>69.46 | 4.92<br>5.08 | | 18.65<br>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) | $C_{13}H_{11}N_3O$ | 69.32<br>68.76 | 4.92<br>5.02 | | 18.65<br>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*) | $C_{21}H_{17}N_3O_3$ | 70 18<br>69.50 | 4.77<br>4.70 | | 11.69<br>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*) | $C_{21}H_{17}N_3O_3$ | 70.18<br>69.89 | 4.77<br>4.79 | | 11.69<br>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 $^1$H 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 condensation of mono- or dialkyl- or dialkenylamine with **5** (Scheme 1 ) provide 5-[[4-[(mono-, dialkyl- or dialkenylamino)alkyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-ones and 11-[[4-[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). The 2- and 4-benzyl-

Table 3

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 their Derivatives **5a-h** (Scheme 1, 5)



**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 | $C_{25}H_{23}BrN_2O_2$ | tetrahydrofuran | 5 |
| **5b** | 1-F | CH | Br | 4 | ethyl acetate-hexane (1:2) | 80-82 | 54 | $C_{25}H_{22}FBrN_2O_2$ | tetrahydrofuran | 4 & room temperature overnight |
| **5c** | 3-F | CH | Br | 4 | ethyl acetate-hexane (1:2) | 80-83 | 39 | $C_{25}H_{22}FBrN_2O_2$ | tetrahydrofuran | 4 & room temperature overnight |
| **5d** | 2-Cl | CH | Cl | 3 | ethyl acetate-hexane (1:2) | 85-90 | 70 | $C_{24}H_{20}Cl_2N_2O_2$ | tetrahydrofuran | 5 |
| **5e** | 2-NH-CO-O-$CH_2C_6H_5$ | CH | Br | 4 | $CHCl_3$-methanol (10:1) | 99-102 | 48 | $C_{33}H_{30}BrN_3O_4$ | tetrahydrofuran | room temperature overnight |
| **5f** | 4-NH-CO-O-$CH_2C_6H_5$ | CH | Br | 4 | ethyl acetate-hexane (1:1) | 63-66 | 38 | $C_{33}H_{30}BrN_3O_4$ | tetrahydrofuran | room temperature overnight |
| **5g** | H | N | Br | 4 | ethyl acetate-hexane (1:1) | 97-102 | 60 | $C_{24}H_{22}BrN_3O_2$ | dioxane | 2 & room temperature overnight |
| **5h** | 8-Cl | N | Br | 4 | ethyl acetate-hexane (1:1) | 75-80 | 41 | $C_{24}H_{21}BrClN_3O_2$ | dioxane | 4 |

Table 4

$^1$H 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)

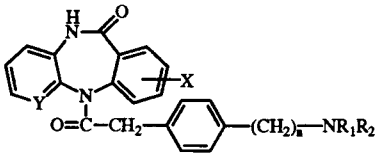
| Compound | $^1$H NMR: δ [a] | Formula | Elemental Analysis Calcd./Found | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | F | N | Br | Cl |
| **5a** | 8.81 (1H , br), 7.95 (1H, d, J = 8.1 Hz), 7.61 (1H, t, J = 7.6 Hz), 7.40 (4H, m), 7.23 (1H, m), 7.07 (4H, m), 6.94 (1H, m), 3.64 (2H, *s*) 3.37 (2H, t, J = 6.7 Hz), 2.53 (2H, m), 1.75 (4H, m) | $C_{25}H_{23}BrN_2O_2$ | 64.80<br>65.21 | 5.00<br>5.11 | | 6.05<br>6.00 | 17.24<br>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) | $C_{25}H_{22}BrFN_2O_2$ | 62.38<br>62.48 | 4.61<br>5.09 | 3.95<br>3.66 | 5.82<br>5.80 | 16.60<br>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) | $C_{25}H_{22}BrFN_2O_2$ | 62.38<br>62.75 | 4.61<br>4.35 | 3.95<br>4.15 | 5.82<br>6.02 | 16.60<br>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) | $C_{24}H_{20}Cl_2N_2O_2$ | 65.61<br>65.12 | 4.59<br>4.84 | | 6.38<br>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) | $C_{33}H_{30}BrN_3O_4$ | 64.71<br>64.68 | 4.94<br>5.08 | | 6.86<br>6.57 | 13.05<br>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) | $C_{33}H_{30}BrN_3O_4$ | 64.71<br>64.41 | 4.94<br>5.26 | | 6.86<br>6.53 | 13.05<br>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) | $C_{24}H_{22}BrN_3O_2$ | 62.08<br>62.70 | 4.78<br>5.36 | | 9.05<br>9.39 | 17.21<br>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) | $C_{24}H_{21}ClBrN_3O_2$ | 57.79<br>57.43 | 4.24<br>4.38 | | 8.42<br>8.15 | 16.01<br>16.42 | 7.10<br>7.45 |

[a] The $^1$H 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-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]benzodiazepin-6-ones, and their Derivatives **6a-p**, **7a-g**, **8b**, **c**, **9b**, **c** (Scheme 1, **6-9**)



**6, 7, 8, 9**

| Compound | X | Y | n | $R_1$ | $R_2$ | Solvent (preparative tlc) Flash Chromatography | Mp (°C) | Yield (%) | Formula | Solvent | Reaction Conditions Reflux (hours) | Reaction Conditions Room Temperature (hours) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | H | CH | 4 | $CH_2$=C($CH_3$)$CH_2$- | $CH_2$=C($CH_3$)$CH_2$- | ethyl acetate-hexane, 1:1 | 47-50 | 34 | $C_{33}H_{37}N_3O_2$ | $CH_3CN$ | 16 | |
| **6b** | 2-NH-CO-O-$CH_2C_6H_5$ | CH | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 10:1 | 77-80 | 18 | $C_{41}H_{48}N_4O_4$ | $CH_3CN$ | 5 | 16 |
| **6c** | 4-NH-CO-O-$CH_2C_6H_5$ | CH | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol,10:1 | 73-77 | 16 | $C_{41}H_{48}N_4O_4$ | $CH_3CN$ | 5 | 16 |
| **6d** | 1-F | CH | 4 | ethyl | ethyl | methanol-$NH_4OH$, 98:2 | 48-55 | 23 | $C_{29}H_{32}FN_3O_2$ | $CH_3CN$ | 72 | |
| **6e** | 1-F | CH | 4 | *i*-propyl | *i*-propyl | methanol-$NH_4OH$, 98:2 | 75-81 | 32 | $C_{31}H_{36}FN_3O_2$ | $CH_3CN$ | 72 | |
| **6f** | 3-F | CH | 4 | ethyl | ethyl | methanol-$NH_4OH$, 98:2 | 57-61 | 42 | $C_{29}H_{32}FN_3O_2$ | $CH_3CN$ | 72 | |
| **6g** | 3-F | CH | 4 | *i*-propyl | *i*-propyl | methanol-$NH_4OH$, 98:2 | 65-72 | 36 | $C_{31}H_{36}FN_3O_2$ | $CH_3CN$ | 72 | |
| **6h** | 3-F | CH | 4 | *i*-butyl | *i*-butyl | methanol-$NH_4OH$, 98:2 | 55-61 | 28 | $C_{33}H_{40}FN_3O_2$ | $CH_3CN$ | 72 | |
| **6i** | 2-Cl | CH | 3 | H | ethyl | methanol-$NH_4OH$, 98:2 | 76-82 | 15 | $C_{26}H_{26}ClN_3O_2$ | $CH_3CN$ | 72 | |
| **6j** | H | CH | 4 | H | ethyl | methanol-$NH_4OH$, 98:2 | 62-65 | 54 | $C_{27}H_{29}N_3O_2$ | $CH_3CN$ | 48 | |
| **6k** | H | N | 4 | ethyl | ethyl | methanol-$NH_4OH$, 98:2 | 49-56 | 38 | $C_{28}H_{32}N_4O_2$ | $CH_3CN$ | 6 | |
| **6l** | H | N | 4 | *i*-propyl | *i*-propyl | methanol-$NH_4OH$, 98:2 | 68-75 | 24 | $C_{30}H_{36}N_4O_2$ | $CH_3CN$ | 16 | |
| **6m** | H | N | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 10:1 | 60-69 | 22 | $C_{32}H_{40}N_4O_2$ | $CH_3CN$ | 6 | |
| **6n** | 8-Cl | N | 4 | ethyl | ethyl | methanol-$NH_4OH$, 98:2 | 60-67 | 62 | $C_{28}H_{31}ClN_4O_2$ | $CH_3CN$ | 16 | |
| **6o** | 8-Cl | N | 4 | *i*-propyl | *i*-propyl | methanol-$NH_4OH$, 98:2 | 68-76 | 18 | $C_{30}H_{35}ClN_4O_2$ | $CH_3CN$ | 16 | |
| **6p** | 8-Cl | N | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 10:1 | 64-69 | 56 | $C_{32}H_{39}ClN_4O_2$ | $CH_3CN$ | 16 | |
| **7a** | H | CH | 3 | ethyl | Pr-$C(Me)_2$-C=O | ethyl acetate-hexane, 1:1 | 72-75 | 68 | $C_{33}H_{39}N_3O_3$ | 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 | 70-79 | 54 | $C_{33}H_{38}ClN_3O_3$ | tetrahydrofuran, $PhNMe_2$ | 1 (dry ice/acetone) | 16 |
| **7c** | H | CH | 4 | ethyl | Pr-$C(Me)_2$-C=O | ethyl acetate-hexane, 1:1 | 60-65 | 62 | $C_{34}H_{41}N_3O_3$ | 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 | 59-70 | 42 | $C_{34}H_{40}ClN_3O_3$ | tetrahydrofuran, $PhNMe_2$ | 1 (dry ice/acetone) | 16 |
| **7e** | H | CH | 4 | *i*-butyl | Pr-C=O | ethyl acetate-hexane, 1:1 | 57-68 | 48 | $C_{33}H_{39}N_3O_3$ | tetrahydrofuran, $PhNMe_2$ | 1 (dry ice/acetone) | 16 |
| **7f** | H | CH | 4 | *i*-butyl | $Me_2$CH-C=O | ethyl acetate-hexane, 1:1 | 80-88 | 32 | $C_{33}H_{39}N_3O_3$ | tetrahydrofuran, $PhNMe_2$ | 1 (dry ice/acetone) | 16 |
| **7g** | H | CH | 4 | *i*-butyl | $Me_2$CH-$CH_2$-C=O | ethyl acetate-hexane, 1:1 | 55-65 | 28 | $C_{34}H_{41}N_3O_3$ | tetrahydrofuran, $PhNMe_2$ | 1 (dry ice/acetone) | 16 |
| **8b** | 2-$NH_2$ | CH | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 10:1 | 92-98 | 85 | $C_{33}H_{42}N_4O_2$ | ethanol | | 72 |
| **8c** | 4-$NH_2$ | CH | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 20:1 | 150-151 | 80 | $C_{33}H_{42}N_4O_2$ | ethanol | | 72 |
| **9b** | 2-I | CH | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 10:1 | 136-141 | 15 | $C_{33}H_{40}IN_3O_2$ | see experimental protocol | | |
| **9c** | 4-I | CH | 4 | *i*-butyl | *i*-butyl | $CHCl_3$-methanol, 10:1 | 67-73 | 12 | $C_{33}H_{40}IN_3O_2$ | see experimental protocol | | |

Table 6

$^1$H 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) | $C_{33}H_{37}N_3O_2$ | 78.07<br>77.63 | 7.35<br>7.17 | | 8.28<br>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) | $C_{41}H_{48}N_4O_4$ | 74.52<br>73.82 | 7.32<br>7.35 | | 8.48<br>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) | $C_{41}H_{48}N_4O_4$ | 74.52<br>74.19 | 7.32<br>7.22 | | 8.48<br>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) | $C_{29}H_{32}FN_3O_2$ | 73.55<br>73.19 | 6.81<br>6.49 | 4.01<br>4.18 | 8.87<br>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) | $C_{31}H_{36}FN_3O_2$ | 74.22<br>73.99 | 7.23<br>7.23 | 3.79<br>3.93 | 8.38<br>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) | $C_{29}H_{32}FN_3O_2$ | 73.55<br>73.34 | 6.81<br>6.93 | 4.01<br>4.07 | 8.87<br>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) | $C_{31}H_{36}FN_3O_2$ | 74.22<br>74.00 | 7.23<br>7.28 | 3.79<br>3.81 | 8.38<br>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) | $C_{33}H_{40}FN_3O_2$ | 74.83<br>74.62 | 7.61<br>7.70 | 3.59<br>3.67 | 7.93<br>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) | $C_{26}H_{26}ClN_3O_2$ | 69.71<br>69.91 | 5.85<br>6.00 | | 7.91<br>7.53 | 9.38<br>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) | $C_{27}H_{29}N_3O_2$ | 75.85<br>75.38 | 6.84<br>6.74 | | 9.83<br>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) | $C_{28}H_{32}N_4O_2$ | 73.66<br>72.82 | 7.06<br>7.04 | | 12.27<br>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) | $C_{30}H_{36}N_4O_2$ | 74.35<br>73.80 | 7.49<br>7.40 | | 11.56<br>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) | $C_{32}H_{40}N_4O_2$ | 74.47<br>74.67 | 7.86<br>7.74 | | 10.93<br>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) | $C_{28}H_{31}ClN_4O_2$ | 68.49<br>68.83 | 6.36<br>6.39 | | 11.42<br>11.12 | 7.22<br>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, 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) | $C_{30}H_{35}ClN_4O_2$ | 69.43<br>69.00 | 6.80<br>6.81 | | 10.79<br>10.53 | 6.83<br>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) | $C_{32}H_{39}ClN_4O_2$ | 70.25<br>70.11 | 7.18<br>7.21 | | 10.24<br>10.17 | 6.48<br>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) | $C_{33}H_{38}N_3O_3$ | 75.40<br>74.90 | 7.48<br>7.43 | | 7.99<br>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) | $C_{33}H_{38}ClN_3O_3$ | 70.76<br>70.79 | 6.84<br>6.90 | | 7.50<br>7.32 | 6.33<br>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) | $C_{34}H_{41}N_3O_3$ | 75.66<br>75.72 | 7.66<br>7.64 | | 7.79<br>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) | $C_{34}H_{40}ClN_3O_3$ | 71.13<br>70.86 | 7.02<br>7.04 | | 7.32<br>7.15 | 6.17<br>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) | $C_{33}H_{39}N_3O_3$ | 75.40<br>74.73 | 7.48<br>7.43 | | 7.99<br>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) | $C_{33}H_{39}N_3O_3$ | 75.40<br>75.56 | 7.48<br>7.49 | | 7.99<br>7.75 | | |

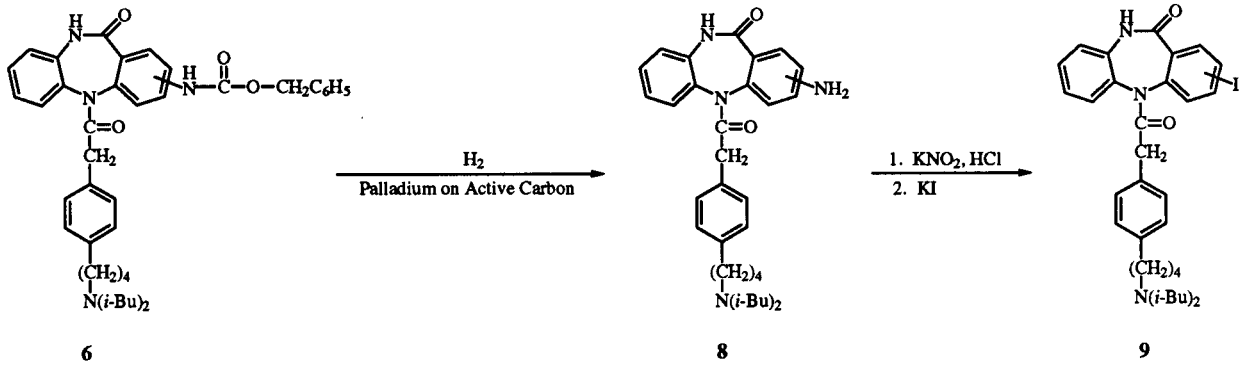
(Continued)

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) | $C_{34}H_{41}N_3O_3$ | 75.66<br>75.18 | 7.66<br>7.64 | | 7.79<br>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) | $C_{33}H_{42}N_4O_2$ | 75.25<br>75.46 | 8.04<br>8.08 | | 10.64<br>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) | $C_{33}H_{42}N_4O_2$ | 75.25<br>75.07 | 8.04<br>8.01 | | 10.64<br>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) | $C_{33}H_{40}IN_3O_2$ | 62.16<br>62.37 | 6.32<br>6.31 | | 6.60<br>6.66 | | 19.90<br>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) | $C_{33}H_{40}IN_3O_2$ | 62.16<br>62.48 | 6.32<br>6.25 | | 6.60<br>6.80 | | 19.90<br>19.79 |

[a] The $^1$H 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-Benzyloxycarbonylamino-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-[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-[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-[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-[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-5*H*-dibenzo-[*b*,*e*][1,4]diazepin-11-one.

Tritiation of 5-[[4-[4-[di(2-methylallyl)amino]butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-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 [$^3$H]5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-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 $C_{18}$ Radial Pak Cartridge in a Z-Module and methanol/0.01 *M* phosphate buffer *p*H 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 [$^3$H]5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one and 5-[[4-[(4-diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one are identical.

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## REFERENCES AND NOTES

[1] P. J. Whitehouse, D. L. Price, A. W. Clark, J. T. Coyle and M. R. Delong, *Ann. Neurol.*, **10**, 122 (1981).

[2] J. T. Coyle, D. L. Price and M. R. Delong, *Science*, **219**, 1184 (1983).

[3] T. A. Slotkin, F. J. Seidler, B. J. Craine, J. M. Bell, G. Bissette and C. B. Neimeroff, *PNAS*, **87**, 2452 (1990).

[4] K. J. Kellar, P. J. Whitehouse, A. N. Martino-Barrows, K. Marcus and D. L. Price, *Brain. Res.*, **436**, 62 (1987).

[5] D. C. Mash, D. D. Flynn and L. T. Potter, *Science*, **228**, 1115 (1985).

[6] R. Quirion, I. Aubert, P. A. Lapchak, R. P. Schaum, S. Teolis, S. Gautier and D. M. Araujo, *Trends Pharm. Sci.*, **Supplement IV**, 80 (1989).

[7] V. I. Cohen, J. Baumgold, B. Jin, R. De la Cruz, W. J. Rzeszotarski and R. C. Reba, *J. Med. Chem.*, **36**, 162 (1993).

[8] V. I. Cohen, B. Jin, M. S. Gitler, R. De la Cruz, S. F. Boulay, B. R. Zeeberg and R. C. Reba, *Eur. J. Med. Chem.*, **30**, 61 (1995).

[9] R. P. Giani, M. Borsa, E. Parini and G. C. A. Tonon, *Synthesis*, 550 (1985).

[10] R. W. Holley and E. Sondheimer, *J. Am. Chem. Soc.*, **76**, 1326 (1954).

[11] W. W. Engel, W. G. Eberlein, G. Mihm, R. Hammer and G. Trummlitz, *J. Med. Chem.*, **32**, 17 (1989).

[12] A. R. Fletcher, J. H. Jones, W. I. Ramage and A. V. Stachulski, *J. Chem. Soc. Perkin Trans. 1*, 2261 (1979).