Synthesis of New 6-(4-Chlorophenyl)perhydro-1,3-diazepine-2,4-diones *via* Ureidobutyric Acids

Jean Guillon [a], Pascal Sonnet [a], Michel Boulouard [b], Patrick Dallemagne [a], Hugues Miel [a], Martine Daoust [b] and Sylvain Rault [a,b]

[a] Centre d'Etudes et de Recherche sur le Médicament de Normandie, Laboratoire de Pharmacochimie, U.F.R. des Sciences Pharmaceutiques, 1 Rue Vaubénard, 14032 Caen, France
[b] Centre d'Etudes et de Recherche sur le Médicament de Normandie, Laboratoire de Pharmacologie, U.F.R. des Sciences Pharmaceutiques, 1 Rue Vaubénard, 14032 Caen, France

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Synthesis of new 6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-diones was accomplished starting from 4-amino-3-(4-chlorophenyl)butyric acid (Baclofen). The chemical pathway involved the cyclisation of various 3-(4-chlorophenyl)-4-ureidobutyric acids. However, none of the new derivatives retained the anticonvulsant activity of their six-membered ring homologues, belonging to the phenylpyrimidinedione series which we recently described.

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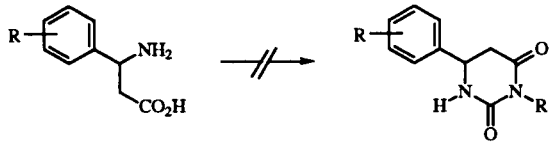
During the course of our work concerning the 3-amino-3-phenylpropionic acid derivatives **1** of therapeutic interest, we reported the synthesis and the anticonvulsant activity of some phenylhexahydropyrimidinediones **2** which exhibited significant affinity towards the benzodiazepine receptor [1] (Scheme 1).

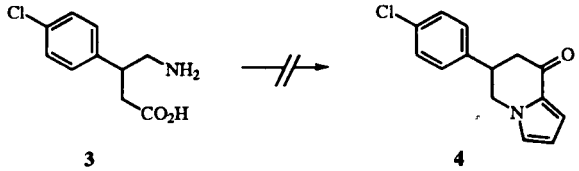
Scheme 1



1 **2**

On the other hand, we have recently undertaken the study of the chemical reactivity of 4-amino-3-(4-chlorophenyl)butyric acid **3** (Baclofen) in the synthesis of new heterocyclic systems such as phenyltetrahydroindolizines **4** [2] (Scheme 2).

Scheme 2

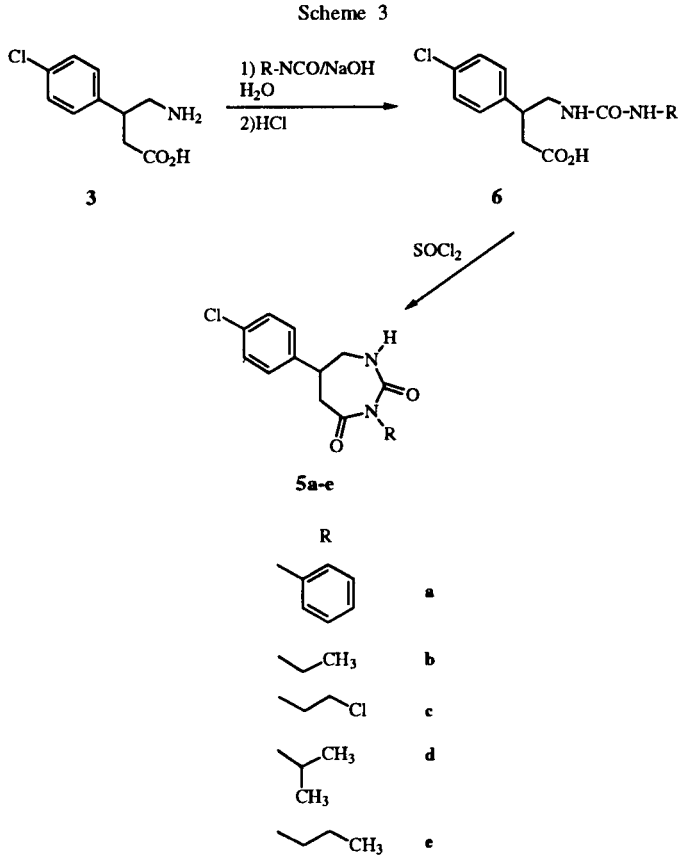


3 **4**

Within this framework, we wanted to check if Baclofen, which itself exerts an agonist activity towards the gaba B receptor, could provide a route to a series of 6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-diones and to observe if these products would preserve the CNS biological properties of their starting material or of their lower homologues, the phenylpyrimidinediones **2**.

Baclofen **3** was treated with an equivalent amount of various isocyanates (phenyl, ethyl, 2-chloroethyl, isopropyl and propylisocyanate) in the presence of an aqueous sodium hydroxide solution at room temperature to yield the sodium salts of the corresponding ureido acids, which remained in solution upon addition of a mineral acid [3,4] that precipitated the ureido acids. The latter were refluxed in thionyl chloride to give, after removal of the solvent, the expected 6-(4-chororophenyl)perhydro-1,3-diazepine-2,4-diones, **5a-e** (Scheme 3).

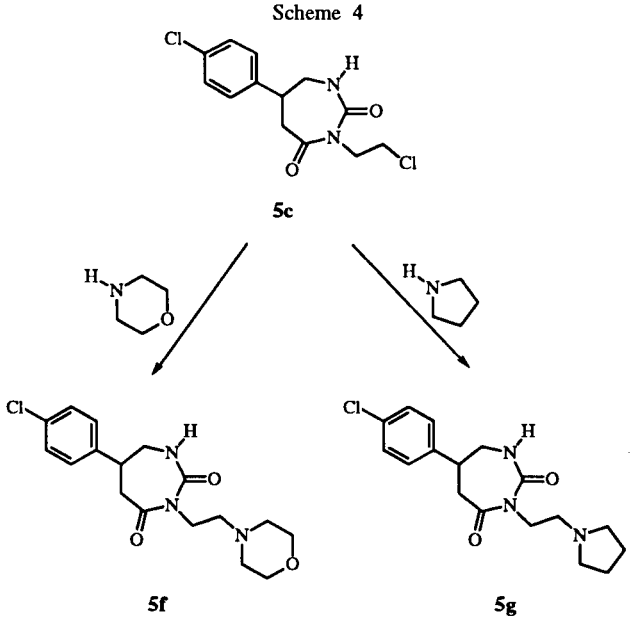
Scheme 3



3 **6** **5a-e**

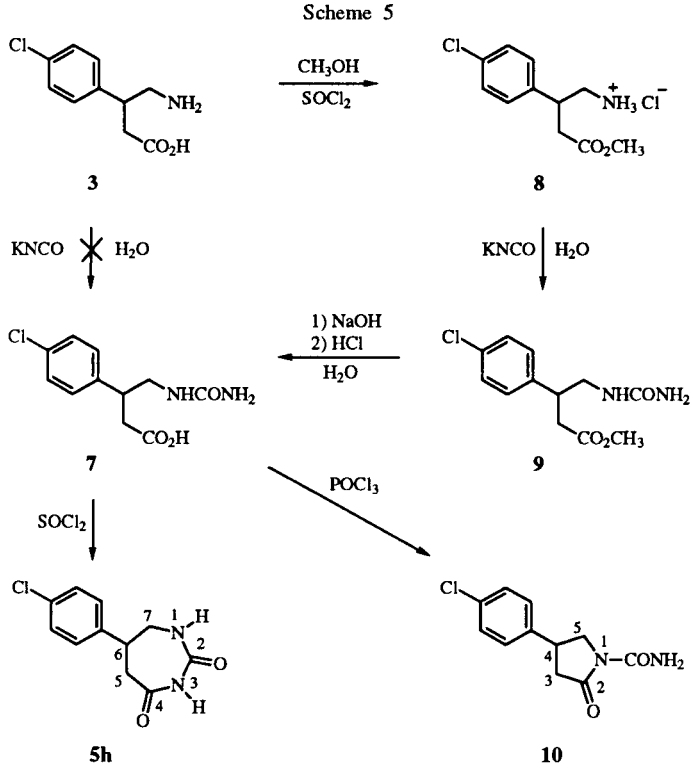
Furthermore, the chloroethyl derivative **5c** was treated with secondary amines such as morpholine and pyrrolidine to give the corresponding tertiary amines **5f** and **5g** (Scheme 4).

Scheme 4



Treatment of Baclofen **3** in water with potassium cyanate did not afford the attempted ureido acid **7**. The latter compound was obtained using the following sequence. Reaction of Baclofen **3** in methanol with a stoichiometric amount of thionyl chloride led to the 2-(4-chlorophenyl)-3-methoxycarbonylpropylammonium chloride **8** in 95% yield [5,6,7]. The action of potassium cyanate (2 equivalents) on derivative **8**, in an aqueous solution, gave ureidoester **9** [8,9]. The hydrolysis of **9** took place in sodium hydroxide solution at 80° and led to the 6-(4-chlorophenyl)-4-ureidobutyric acid **7** after final acidification with dilute hydrochloric acid. Cyclisation of the ureido acid **7** was then accomplished by refluxing with thionyl chloride as described above to give the 6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5h** in 82% yield. Replacement of thionyl chloride by phosphorus oxychloride in the latter reaction led to the 2-oxopyrrolidine-1-carboxamide **10** in 60% yield [10,11] (Scheme 5).

Scheme 5



It is unfortunate and in contrast to the previously described phenylpyrimidinediones **2**, none of the phenylperhydrodiazepinediones **5a-h** possessed neither benzodiazepine receptor affinity nor anticonvulsant activity.

EXPERIMENTAL

General Methods.

Melting points were determined on a Köfler block and are uncorrected. Infrared spectra were recorded on a Unicam Mattson 1000 apparatus and only significant absorptions in reciprocal centimeters are listed. The nmr spectra were recorded on a Jeol JNM-LA 400 using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm downfield (δ) from tetramethylsilane.

General Procedure for the Preparation of 3-(4-Chlorophenyl)-4-(3-phenylureido)butyric Acid **6a** and 4-(3'-Alkylureido)-3-(4-chlorophenyl)butyric Acids **6b-e**.

Baclofen **3** (0.1 mole) was dissolved in an aqueous solution of sodium hydroxide (120 ml, 1 *N*) and then phenylisocyanate or alkylisocyanate (0.1 mole) was added to the reaction mixture which was stirred at room temperature for 1 hour. The solution was filtered and acidified to *p*H = 1 with dilute hydrochloric acid. The precipitate was filtered, washed with water and dried to give **6a-e**.

3-(4-Chlorophenyl)-4-(3-phenylureido)butyric Acid **6a**.

Compound **6a** was obtained as white crystals (75%), mp 154°; ir (potassium bromide): 3400-3200 (OH), 3360 (NH), 1710, 1660 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 12.05 (bs, OH), 8.37 (s, NH), 7.38-6.88 (m, 9H-φ), 6.05 (t, $J_{NH\ H-4}$ = 5.6 Hz, NH), 3.42 (m, H-3), 3.25 (m, H-4), 2.70 (dd, $J_{H-2a\ H-2b}$ = 16.0 Hz, $J_{H-2a\ H-3}$ = 5.2 Hz, H-2a), 2.50 (dd, $J_{H-2b\ H-2a}$ = 16.0 Hz, $J_{H-2b\ H-3}$ = 8.8 Hz, H-2b).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_3$: C, 61.35; H, 5.14; N, 8.41. Found: C, 61.18; H, 5.10; N, 8.35.

3-(4-Chlorophenyl)-4-(3-ethylureido)butyric Acid **6b**.

This product was a colorless oil (45%); ir (potassium bromide): 3400-3200 (OH), 3340 (NH), 1755, 1650 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 12.05 (bs, OH), 7.38 (d, $J_{H-3'\ H-2'}$ = $J_{H-5\ H-6'}$ = 8.5 Hz, H-3' and H-5'), 7.28 (d, $J_{H-2'\ H-3'}$ = $J_{H-6'\ H-5'}$ =

8.5 Hz, H-2' and H-6'), 5.80 (m, 2NH), 3.29 (m, H-3), 3.18 (m, H-4), 3.01 (m, CH_2), 2.68 (dd, $J_{H\text{-}2a\ H\text{-}2b}$ = 16.0 Hz, $J_{H\text{-}2a\ H\text{-}3}$ = 4.6 Hz, H-2a), 2.52 (dd, $J_{H\text{-}2b\ H\text{-}2a}$ = 16.0 Hz, $J_{H\text{-}2b\ H\text{-}3}$ = 8.8 Hz, H-2b), 0.99 (t, J_{CH3CH2} = 7.2 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{17}ClN_2O_3$: C, 54.83; H, 5.97; N, 9.84. Found: C, 54.71; H, 5.84; N, 9.73.

3-(4-Chlorophenyl)-4-[3-(2-chloroethyl)ureido]butyric Acid **6c**.

This product was a colorless oil (89%); ir (potassium bromide): 3400-3200 (OH), 3360 (NH), 1755, 1635 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 12.02 (bs, OH), 7.30 (d, $J_{H\text{-}3'\ H\text{-}2'}$ = $J_{H\text{-}3'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.23 (d, $J_{H\text{-}2'\ H\text{-}3'}$ = $J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 6.13 (t, $J_{NH\ H\text{-}4}$ = 5.5 Hz, NH), 6.00 (t, J_{NHCH2} = 5.5 Hz, NH), 3.51 (t, J_{CH2CH2} = 6.2 Hz, CH_2), 3.30 (m, H-3 and CH_2), 3.10 (m, H-4), 2.60 (dd, $J_{H\text{-}2a\ H\text{-}2b}$ = 15.8 Hz, $J_{H\text{-}2a\ H\text{-}3}$ = 4.7 Hz, H-2a), 2.50 (dd, $J_{H\text{-}2b\ H\text{-}2a}$ = 15.8 Hz, $J_{H\text{-}2b\ H\text{-}3}$ = 8.8 Hz, H-2b).

Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_3$: C, 48.90; H, 5.01; N, 8.78. Found: C, 48.74; H, 5.27; N, 8.55.

3-(4-Chlorophenyl)-4-(3-isopropylureido)butyric Acid **6d**.

This compound was obtained as a colorless oil (40%); ir (potassium bromide): 3400-3200 (OH), 3330 (NH), 1760, 1650 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 12.05 (bs, OH), 7.32 (d, $J_{H\text{-}3'\ H\text{-}2'}$ = $J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.21 (d, $J_{H\text{-}2'\ H\text{-}3'}$ = $J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 5.57 (m, 2 NH), 3.65 (m, CH), 3.25 (m, H-3), 3.13 (m, H-4), 2.60 (dd, $J_{H\text{-}2a\ H\text{-}2b}$ = 16.0 Hz, $J_{H\text{-}2a\ H\text{-}3}$ = 4.2 Hz, H-2a), 2.42 (dd, $J_{H\text{-}2b\ H\text{-}2a}$ = 16.0 Hz, $J_{H\text{-}2b\ H\text{-}3}$ = 8.8 Hz, H-2b), 1.33 (m, CH_2), 0.95 (d, J_{CH3CH} = 5.9 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{19}ClN_2O_3$: C, 56.28; H, 6.36; N, 9.38. Found: C, 56.55; H, 6.29; N, 9.32.

3-(4-Chlorophenyl)-4-(3-propylureido)butyric Acid **6e**.

This compound was obtained as a colorless oil (63%); ir (potassium bromide): 3400-3200 (OH), 3380 (NH), 1760, 1650 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 12.01 (bs, OH), 7.32 (d, $J_{H\text{-}3'\ H\text{-}2'}$ = $J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.22 (d, $J_{H\text{-}2'\ H\text{-}3'}$ = $J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 5.76 (t, $J_{NH\ H\text{-}4}$ = 5.5 Hz, NH), 5.68 (t, J_{NHCH2} = 5.5 Hz, NH), 3.23 (m, H-3), 3.11 (m, H-4), 2.87 (m, CH_2), 2.61 (dd, $J_{H\text{-}2a\ H\text{-}2b}$ = 16.0 Hz, $J_{H\text{-}2a\ H\text{-}3}$ = 4.6 Hz, H-2a), 2.42 (dd, $J_{H\text{-}2b\ H\text{-}2a}$ = 16.0 Hz, $J_{H\text{-}2b\ H\text{-}3}$ = 8.8 Hz, H-2b), 1.33 (m, CH_2), 0.80 (t, J_{CH3CH2} = 7.5 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{19}ClN_2O_3$: C, 56.28; H, 6.36; N, 9.38. Found: C, 56.42; H, 6.51; N, 9.45.

General Procedure for the Preparation of 6-(4-Chlorophenyl)-3-phenylperhydro-1,3-diazepine-2,4-dione **5a**, 3-Alkyl-6-(4-chlorophenyl)perhydro-1,3-dizepine-2,4-diones **5b-e** and 6-(4-Chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5h**.

A solution of 3-(4-chlorophenyl)-4-(3-phenylureido)butyric acid **6a**, 3-(4-chlorophenyl)-4-(3-alkylureido)butyric acid **6b-e** or 3-(4-chlorophenyl)-4-ureidobutyric acid **7** (0.02 mole) in thionyl chloride (40 ml) was refluxed for 30 minutes and evaporated to dryness. The solid residue was then triturated with water, filtered and dried to give **5a-e** and **5h**.

6-(4-Chlorophenyl)-3-phenylperhydro-1,3-diazepine-2,4-dione **5a**.

This compound was obtained as white crystals (85%), mp 128°; ir (potassium bromide): 3230 (NH), 1710, 1690 (CO); ^{1}H-nmr (deuteriochloroform): 10.40 (s, NH), 7.40 (m, 6 H-ϕ), 7.17 (m, 2 H-ϕ), 7.09 (m, 1 H-ϕ), 4.39 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.7 Hz, H-7a), 3.83 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.60 (m, H-6), 3.05 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.0 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.6 Hz, H-5a), 2.80 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.0 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 9.1 Hz, H-5b); ^{13}C-nmr (deuteriochloroform): 175.6 (C-4), 149.7 (C-2), 138.7 (C-1"), 137.2 (C-1'), 133.3 (C-4'), 129.1 (C-2' and C-6'), 128.9 (C-3" and C-5"), 127.9 (C-3' and C-5'), 124.1 (C-4"), 120.0 (C-2" and C-6"), 51.8 (C-7), 40.7 (C-6), 35.3 (C-5).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.86; H, 4.80; N, 8.89. Found: C, 64.51; H, 4.65; N, 8.82.

6-(4-Chlorophenyl)-3-ethylperhydro-1,3-diazepine-2,4-dione **5b**.

This compound was obtained as white crystals (90%), mp 106°; ir (potassium bromide): 3335 (NH), 1725, 1700 (CO); ^{1}H-nmr (deuteriochloroform): 8.30 (s, NH), 7.33 (d, $J_{H\text{-}3'\ H\text{-}2'}$ = $J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.16 (d, $J_{H\text{-}2'\ H\text{-}3'}$ = $J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 4.30 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.3 Hz, H-7a), 3.77 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.55 (m, H-6), 3.35 (q, J_{CH2CH3} = 7.1 Hz, CH_2), 2.96 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.0 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.4 Hz, H-5a), 2.75 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.0 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 9.2 Hz, H-5b), 1.20 (t, J_{CH3CH2} = 7.1 Hz, CH_3); ^{13}C-nmr (deuteriochloroform): 175.2 (C-4), 152.4 (C'-2), 139.1 (C-1'), 132.7 (C-4'), 129.2 (C-2' and C-6'), 127.9 (C-3' and C'-5'), 52.1 (C-7), 40.6 (C-6), 35.4 (C-5), 34.7 (CH_2), 14.8 (CH_3).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.66; N, 10.50. Found: C, 58.38; H, 5.60; N, 10.45.

3-(2-Chloroethyl)-6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5c**.

This compound was obtained as white crystals (76%), mp 86°; ir (potassium bromide): 3330 (NH), 1700, 1680 (CO); ^{1}H-nmr (deuteriochloroform): 8.70 (s, NH), 7.34 (d, $J_{H\text{-}3'\ H\text{-}2'}$ = $J_{H\text{-}5'\ H\text{-}6'}$ = 8.4 Hz, H-3' and H-5'), 7.17 (d, $J_{H\text{-}2'\ H\text{-}3'}$ = $J_{H\text{-}6'\ H\text{-}5'}$ = 8.4 Hz, H-2' and H-6'), 4.31 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.3 Hz, H-7a), 3.78 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.63 (m, 2 CH_2), 3.55 (m, H-6), 3.00 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.0 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.5 Hz, H-5a), 2.76 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.0 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 9.3 Hz, H-5b); ^{13}C-nmr (deuteriochloroform): 175.3 (C-4), 152.5 (C-2), 138.8 (C-1'), 133.2 (C-4'), 129.1 (C-2' and C-6'), 127.9 (C-3' and C-5'), 51.8 (C-7), 43.2 (CH_2), 41.7 (CH_2), 40.5 (C-6), 35.5 (C-5).

Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_2$: C, 51.84; H, 4.68; N, 9.30. Found: C, 51.58; H, 4.48; N, 9.19.

6-(4-Chlorophenyl)-3-isopropylperhydro-1,3-diazepine-2,4-dione **5d**.

This compound was obtained as white crystals (76%), mp 102°; ir (potassium bromide): 3230 (NH), 1700, 1680 (CO); ^{1}H-nmr (deuteriochloroform): 8.13 (s, NH), 7.24 (d, $J_{H\text{-}3'\ H\text{-}2'}$ = $J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.07 (d, $J_{H\text{-}2'\ H\text{-}3'}$ = $J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 4.22 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.2 Hz, H-7a), 3.93 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.66 (m, CH), 3.47 (m, H-6), 2.91 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.3 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.3 Hz, H-5a), 2.63 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.3 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 8.8 Hz, H-5b), 1.13 (d, J_{CH3CH} = 6.4 Hz, CH_3); ^{13}C-nmr (deuteriochloroform): 175.1 (C-4), 151.5 (C-2), 139.0 (C-1'), 133.1 (C-4'), 129.0 (C-2' and C-6'), 127.9 (C-3' and C-5'), 51.7 (C-7), 41.9 (CH), 40.6 (C-6), 35.3 (C-5), 22.7 (CH_3).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.97. Found: C, 59.52; H, 6.03; N, 9.84.

6-(4-Chlorophenyl)-3-propylperhydro-1,3-diazepine-2,5-dione **5e**.

This compound was obtained as white crystals (64%), mp 96°; ir (potassium bromide): 3230 (NH), 1700, 1680 (CO); ^{1}H-nmr (deuteriochloroform): 8.30 (s, NH), 7.32 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.16 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 4.30 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.2 Hz, H-7a), 3.77 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.55 (m, H-6), 3.26 (m, CH_2), 2.98 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.3 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.4 Hz, H-5a), 2.76 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.3 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 9.2 Hz, H-5b), 1.60 (m, CH_2), 0.95 (t, J_{CH3CH2} = 7.3 Hz, CH_3); ^{13}C-nmr (deuteriochloroform): 175.2 (C-4), 152.5 (C-2), 139.0 (C-1'), 133.1 (C-4'), 129.1 (C-2' and C-6'), 127.9 (C-3' and C-5'), 51.8 (C-7), 41.5 (CH_2), 40.5 (C-6), 35.4 (C-5), 22.7 (CH_2), 11.3 (CH_3).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.97. Found: C, 59.92; H, 5.97; N, 9.76.

6-(4-Chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5h**.

This compound was obtained as white crystals (82%), mp 156°; ir (potassium bromide): 3360 (NH), 1740, 1705 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 8.15 (s, NH), 7.32 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'}$ = 8.4 Hz, H-3' and H-5'), 7.17 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'}$ = 8.4 Hz, H-2' and H-6'), 5.81 (s, NH), 4.29 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.2 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.1 Hz, H-7a), 3.76 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.2 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.57 (ddd, $J_{H\text{-}6\ H\text{-}7a} = J_{H\text{-}6\ H\text{-}7b}$ = 8.1 Hz, $J_{H\text{-}6\ H\text{-}5a} = J_{H\text{-}6\ H\text{-}5b}$ = 8.5 Hz, H-6), 3.00 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.6 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.5 Hz, H-5a), 2.73 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.6 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 8.5 Hz, H-5b); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 175.2 (C-4), 153.1 (C-2), 138.9 (C-1'), 1332 (C-4'), 129.0 (C-2' and C-6'), 127.9 (C-3' and C-5'), 51.5 (C-6), 40.4 (C-7), 35.3 (C-5).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.34; H, 4.61; N, 11.74. Found: C, 55.21; H, 4.55; N, 11.63.

General Procedure for the Preparation of 3-(2-Morpholinoethyl)-6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5f** and 3-(2-Pyrrolidinoethyl)-6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5g**.

A solution of 3-(2-chloroethyl)-6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5c** (0.003 mole) in morpholine or pyrrolidine (15 ml) was refluxed for 2 hours. The excess solvent was evaporated to dryness, the residual oil was triturated with water to give crystals which were filtered, washed, dried and recrystallized from diethyl ether.

3-(2-Morpholinoethyl)-6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5f**.

This compound was obtained as yellow crystals (27%), mp 96°; ir (potassium bromide): 3310 (NH), 1700, 1675 (CO); ^{1}H-nmr (deuteriochloroform): 8.60 (bs, NH), 7.26 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.09 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 4.22 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.4 Hz, H-7a), 3.71 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.2 Hz, H-7b), 3.62 (t, J_{CH2CH2} = 4.4 Hz, CH_2), 3.48 (m, H-6), 3.35 (t, J_{CH2CH2} = 6.3 Hz, CH_2), 2.94 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.4 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.6 Hz, H-5a), 2.67 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.4 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 9.3 Hz, H-5b), 2.46 (t, J_{CH2CH2} = 6.3 Hz, CH_2), 2.41 (m, 2 CH_2); ^{13}C-nmr (deuteriochloroform): 175.1 (C-4), 152.4 (C-2), 139.0 (C-1'), 133.1 (C-4'), 129.0 (C-2' and C-6'), 127.9 (C-3' and C-5'), 66.9 (2 CH_2O), 53.3 (CH_2N), 51.7 (C-7), 40.6 (C-6), 36.5 (CH_2), 35.4 (C-5).

Anal. Calcd. for $C_{17}H_{22}ClN_3O_3$: C, 58.03; H, 6.30; N, 11.94. Found: C, 57.89; H, 6.20; N, 11.77.

3-(2-Pyrrolidinoethyl)-6-(4-chlorophenyl)perhydro-1,3-diazepine-2,4-dione **5g**.

This compound was obtained as yellow crystals (58%), mp 102°; ir (potassium bromide): 3380 (NH), 1700, 1675 (CO); ^{1}H-nmr (deuteriochloroform): 8.40 (bs, NH), 7.26 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'}$ = 8.5 Hz, H-3' and H-5'), 7.05 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'}$ = 8.5 Hz, H-2' and H-6'), 4.19 (dd, $J_{H\text{-}7a\ H\text{-}7b}$ = 11.0 Hz, $J_{H\text{-}7a\ H\text{-}6}$ = 8.2 Hz, H-7a), 3.64 (dd, $J_{H\text{-}7b\ H\text{-}7a}$ = 11.0 Hz, $J_{H\text{-}7b\ H\text{-}6}$ = 8.1 Hz, H-7b), 3.45 (m, H-6), 3.32 (t, J_{CH2CH2} = 6.3 Hz, CH_2), 2.85 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 17.2 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8.5 Hz, H-5a), 2.61 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 17.2 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 9.3 Hz, H-5b), 2.51 (t, J_{CH2CH2} = 6.3 Hz, CH_2), 2.42 (m, 2 CH_2-α-pyrrolidine), 1.65 (m, 2 CH_2-β-pyrrolidine); ^{13}C-nmr (deuteriochloroform): 174.9 (C-4), 152.0 (C-2), 138.8 (C-1'), 132.6 (C-4'), 128.6 (C-2' and C-6'), 127.5 (C-3' and C-5'), 53.5 (2 CH_2N), 51.3 (C-7), 42.9 (CH_2), 41.2 (C-6), 40.1 (CH_2), 35.0 (C-5), 23.1 (CH_2).

Anal. Calcd. for $C_{17}H_{22}ClN_3O_2$: C, 60.80; H, 6.60; N, 12.51. Found: C, 60.58; H, 6.35; N, 12.35.

2-(4-Chlorophenyl)-3-methoxycarbonylpropylammonium Chloride **8**.

To a suspension of Baclofen **3** (10 g, 0.048 mole) in methanol (100 ml) was added thionyl chloride (5.68 g, 0.048 mole). The reaction mixture was stirred at room temperature for 30 minutes, then evaporated to dryness under reduced pressure. The residue was triturated in diethyl ether until crystallization, the precipitate was filtered, washed with diethyl ether and dried to give white crystals (98%), mp 148°; ir (potassium bromide): 3050-2750 (NH_3+), 1730 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 8.28 (bs, NH_3+), 7.34 (m, H-2', H-3', H-5' and H-6'), 3.44 (s, CH_3), 3.09 (m, H-3), 2.97 (m, H-4 and H-2a), 2.67 (m, H-2b); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 171.2 (CO), 139.1 (C-1'), 131.8 (C-4'), 129.8 (C-2' and C-6'), 128.5 (C-3' and C-5'), 51.4 (CH_3), 43.0 (C-3), 38.9 (C-4), 37.4 (C-2).

Anal. Calcd. for $C_{11}H_{15}Cl_2NO_2$: C, 50.07; H, 5.68; N, 5.30. Found: C, 49.92; H, 5.79; N, 5.14.

3-(4-Chlorophenyl)-4-ureidobutyric Acid Methyl Ester **9**.

To a solution of 2-(4-chlorophenyl)-3-methoxycarbonylpropylammonium chloride **8** (13 g, 0.05 mole) in water (100 ml) was added potassium cyanate (8.12 g, 0.1 mole). The reaction mixture was stirred at room temperature for 6 hours, then extracted with methylene chloride (100 ml). The organic layer was separated and the aqueous layer extracted with methylene chloride (100 ml). The combined organic layer was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give **9** as white crystals (78%), mp 61°; ir (potassium bromide): 3450, 3360, 3240 (NH, NH_2), 1725, 1670 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.26 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'}$ = 8.14 Hz, H-3' and H-5'), 7.17 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'}$ = 8.14 Hz, H-2' and H-6'), 6.03 (t, $J_{NH\ H\text{-}4}$ = 4.35 Hz, NH), 5.43 (bs, NH_2), 3.40 (s, CH_3), 3.08 (m, H-3 and H-4), 2.65 (dd, $J_{H\text{-}2a\ H\text{-}2b}$ = 15.85 Hz, $J_{H\text{-}2a\ H\text{-}3}$ = 3.60 Hz, H-2a), 2.47 (dd, $J_{H\text{-}2b\ H\text{-}2a}$ = 15.85 Hz, $J_{H\text{-}2b\ H\text{-}3}$ = 7.70 Hz, H-2b); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 171.9 (C-1), 158.7 (CO), 141.2 (C-1'), 131.0 (C-4'), 129.5 (C-2' and C-6'), 128.3 (C-3' and C-5'), 51.2 (CH_3), 44.3 (C-3), 41.8 (C-4), 37.4 (C-2).

Anal. Calcd. for $C_{12}H_{15}ClN_2O_3$: C, 53.23; H, 5.54; N, 10.35. Found: C, 53.37; H, 5.61; N, 10.47.

3-(4-Chlorophenyl)-4-ureidobutyric Acid **7**.

A suspension of 3-(4-chlorophenyl)-4-ureidobutyric acid methyl ester **9** (6.5 g, 0.036 mole) in an aqueous solution of sodium hydroxide (100 ml, 10%) was heated at 80° for 1 hour. After cooling, the reaction mixture was filtered and acidified until *p*H = 1 with an aqueous solution of hydrochloric acid (20%). The precipitate was filtered, washed with water and dried to give **7** as white crystals (75%), mp 195°; ir (potassium bromide): 3385, 3360, 3225 (NH, NH_2), 3300-2570 (OH), 1725, 1650 (CO); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 12.10 (bs, OH), 7.36 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'} = 8.0$ Hz, H-3' and H-5'), 7.26 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'} = 8.0$ Hz, H-2' and H-6'), 5.95 (t, $J_{NH\ H\text{-}4} = 5.1$ Hz, NH), 5.46 (bs, NH_2), 3.22 (m, H-3), 3.14 (m, H-4), 2.63 (dd, $J_{H\text{-}2a\ H\text{-}2b} = 15.7$ Hz, $J_{H\text{-}2a\ H\text{-}3} = 4.0$ Hz, H-2a), 2.47 (dd, $J_{H\text{-}2b\ H\text{-}2a} = 15.7$ Hz, $J_{H\text{-}2b\ H\text{-}3} = 9.1$ Hz, H-2b); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 173.1 (C-1), 158.7 (CO), 141.6 (C-1'), 131.0 (C-4'), 129.7 (C-2' and C-6'), 128.2 (C-3' and C-5'), 44.4 (C-3), 41.8 (C-4), 37.8 (C-2).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.46; H, 5.07; N, 10.91. Found: C, 51.55; H, 4.91; N, 11.14.

4-(4-Chlorophenyl)-2-oxopyrrolidine-1-carboxamide **10**.

A suspension of 3-(4-chlorophenyl)-4-ureidobutyric acid **7** (0.8 g, 0.0032 mole) in phosphorus oxychloride (10 ml) was stirred at room temperature for 6 hours. The excess of phosphorus oxychloride was evaporated under reduced pressure. The residue was triturated in water then extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium hydrogenocarbonate, dried over calcium chloride and evaporated to dryness under reduced pressure to give **10** as a yellow oil (60%); ir (potassium bromide): 3395, 3320 (NH_2), 1705, 1630 (CO); ^{1}H-nmr (deuteriochloroform): 8.03 (s, NH), 7.21 (d, $J_{H\text{-}3'\ H\text{-}2'} = J_{H\text{-}5'\ H\text{-}6'} = 8.6$ Hz, H-3' and H-5'), 7.07 (d, $J_{H\text{-}2'\ H\text{-}3'} = J_{H\text{-}6'\ H\text{-}5'} = 8.6$ Hz, H-2' and H-6'), 5.99 (s, NH), 4.17 (m, H-4), 3.66 (m, H-5a), 3.44 (m, H-5b), 2.88 (dd, $J_{H\text{-}3a\ H\text{-}3b} = 17.2$ Hz, $J_{H\text{-}3a\ H\text{-}4} = 8.8$ Hz, H-3a), 2.64 (dd, $J_{H\text{-}3b\ H\text{-}3a} = 17.2$ Hz, $J_{H\text{-}3b\ H\text{-}4} = 8.8$ Hz, H-3b); ^{13}C-nmr (deuteriochloroform): 175.1 (C-2), 153.0 (CO), 138.7 (C-1'), 132.9 (C-4'), 128.8 (C-2' and C-6'), 127.8 (C-3' and C-5'), 51.8 (C-3), 40.1 (C-4), 35.0 (C-2).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.34; H, 4.61; N, 11.74. Found: C, 55.39; H, 4.81; N, 12.02.

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