Synthesis of 6,7,8,9-Tetrahydro-5*H*-pyrimido-[4,5-*b*][1,4]diazepine-6,8-diones

Oludotun A. Phillips and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta,
Edmonton, Alberta, Canada T6G 2N8

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The sodium ethoxide catalyzed condensation of 4,5-diaminopyrimidine (**3**) with diethyl malonate afforded 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**). Methylation of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**) using sodium hydride and two equivalents of iodomethane gave 5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**5**) which on further methylation using sodium hydride and one equivalent iodomethane yielded 6,7,8,9-tetrahydro-5,7,9-trimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**6**). Reaction of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**) with 4.2 equivalents of sodium hydride and 4.1 equivalents of iodomethane afforded 6,7,8,9-tetrahydro-5,7,7,9-tetramethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**7**). 6,7,8,9-Tetrahydro-5,7,7,9-tetramethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**7**) exhibited weak anticonvulsant activities in the subcutaneous pentylenetetrazole and maximal electroshock anticonvulsant screens indicating it is a partial bioisostere of the anticonvulsant drug clobazam (**2**).

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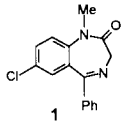
Introduction.

The 1,4-benzodiazepin-2-one class of compounds have an established role in the treatment of epileptic seizures. Diazepam (**1**) is used in the management of status epilepticus and several related 1,4-benzodiazepin-2-ones are employed in the long term management of intractable seizures [1]. More recently, 1,5-benzodiazepines such as clobazam (**2**) have demonstrated efficacy in generalized and focal epilepsies as a singular or adjuvant drug in patients which are resistent or refractory to other anticonvulsant drugs [2,3]. However, the clinical value of diazepam and clobazam may not be as great as desired due to neurological side effects and/or re-appearance of seizures after a few weeks or months of therapy due to the development of tolerance [3,4].



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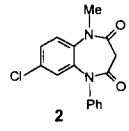

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The requirement for an electronegative substituent at C-7 of 1,4-benzodiazepin-2-ones such as **1** [5,6], and the structurally related 1,5-benzodiazepine-2,4-dione (**2**), is well documented. It was therefore of interest to prepare 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-diones **4-7** which are electronically analogous to the chlorophenyl analog **2** since they possess similar electron-density profiles at equivalent positions. When the inductive and resonance effects of the chloro substituent **2** and the ring nitrogens in the pyrimido compounds **4-7** are compared, the resulting electron-densities are qualitatively similar for the chlorophenyl and pyrimido ring systems at equivalent positions as illustrated in Figure 1. This study was therefore initiated to determine whether the chlorophenyl and pyrimido rings are bioisosteric with respect to anticonvulsant activities since these ring systems are similar in size and shape, and they possess similar electron-density profiles at equivalent positions. Thus, it could be expected that these chlorophenyl and pyrimido classes of compounds could interact with the same receptor site(s) to exhibit anticonvulsant activity.

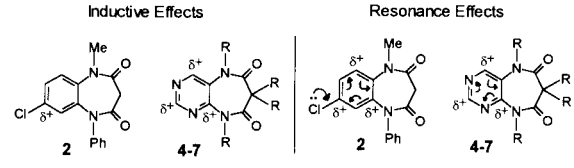


Figure 1. A comparison of the inductive and resonance effects exhibited by the chloro substituent in chlorobenzenes **2** and the ring nitrogens in pyrimidines **4-7**.

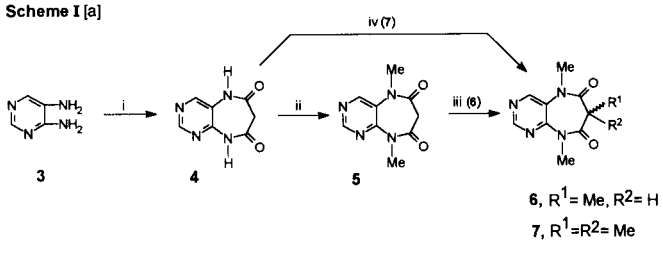
Chemistry.

Reaction of 4,5-diaminopyrimidine (**3**) with diethyl malonate and sodium ethoxide in dry xylene at reflux temperature afforded 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**) in 64% yield. In contrast, a similar reaction of 4,5-diaminopyrimidine (**3**) with malonyl chloride, either with or without diethylamine, yielded intractable material. Treatment of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**) with 2.5 equivalents sodium hydride in dimethylformamide and then reaction with two equivalents of iodomethane gave 5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**5**) in 60% yield. Monomethylation of 5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**5**) using 1.45 equivalents sodium hydride and one equivalent iodomethane yielded 6,7,8,9-tetrahydro-5,7,9-trimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**6**) in 65% yield. Alternatively, reaction of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**) with 4.2 equivalents sodium hydride and then treatment with 4.1 equivalents iodomethane afforded 6,7,8,9-tetrahydro-5,7,7,9-tetrameth-

yl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**7**, 46%).

An attempt to prepare 9-phenyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione by the reaction of 5-amino-4-anilinopyrimidine [7] with diethyl malonate and sodium ethoxide, using a procedure similar to that employed for the conversion of 4,5-diaminopyrimidine (**3**) to 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**), was unsuccessful since an intractable product was obtained.

Scheme I [a]



[a] Reagents: i) $CH_2(CO_2Et)_2$, NaOEt, dry xylene, reflux; ii) 2.5 equivalents NaH, 2.0 equivalents MeI, DMF-Et_2O, 0°; iii) 1.45 equivalents NaH, 1 equivalent MeI, DMF-Et_2O, 0°; iv) 4.2 equivalents NaH, 4.1 equivalents MeI, DMF-Et_2O, 0°.

Anticonvulsant Test Results.

The anticonvulsant activities of the 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-diones **4**,**7** against subcutaneous pentylenetetrazole (scPTZ) and maximal electroshock (MES) induced seizures, which are models for absence (petit mal) and generalized tonic clonic (grand mal) epilepsy, respectively were determined [8]. The unsubstituted **4**, 5,9-dimethyl **5** and 5,7,9-trimethyl **6** analogs of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione were all inactive in both the scPTZ and MES screens at a 300 mg/kg intraparietoneal (ip) dose at both thirty minutes and four hours postinjection of the test compound. In contrast, 6,7,8,9-tetrahydro-5,7,7,9-tetramethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**7**) was a partial bioisostere of clobazam since it protected one out of one mice in the MES test at both thirty minutes and four hours, and two out of four mice in the scPTZ test at four hours for a 300 mg/kg ip dose. The ED_{50} values for the standard reference drugs in these screens were clonazepam (scPTZ, ED_{50} = 0.02 mg/kg; MES, ED_{50} = 86.6 mg/kg) and valproic acid (scPTZ, ED_{50} = 148.6 mg/kg; MES, ED_{50} = 271.7 mg/kg).

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover apparatus, and are uncorrected. Nuclear magnetic resonance spectra (^{1}H nmr) were recorded on a Bruker AM-300 spectrometer. Mass spectra were determined on a Hewlett-Packard 5995A mass spectrometer. Infrared spectra were acquired using a Nicolet 5DX FT spectrometer. Preparative thin layer chromatogaphy was performed on Camag Kieselgel DSF silica gel plates, 1.0 mm in thickness.

6,7,8,9-Tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**).

A mixture of 4,5-diaminopyrimidine (**3**, 2.0 g, 18.2 mmoles), diethyl malonate (2.91 g, 18.2 mmoles) and sodium ethoxide (2.93 g, 43.0 mmoles) in dry xylene (60 ml) was heated at reflux for twenty hours under a nitrogen atmosphere. After cooling to 25°, the solvent was removed *in vacuo*, the yellow residue obtained was dissolved in water (150 ml) and the filtrate was acidified to *p*H 5 using 50% aqueous hydrogen chloride with ice-bath cooling. The precipitate was filtered off, washed with water, dried and then recrystallized from dimethyl sulfoxide:methanol (1:10, v/v) to afford 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**, 2.07 g, 64%), mp 290-291° dec; ir (potassium bromide): ν 3103 (NH), 1688 (C=O) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.36 (br s, 1H, N^9-H, exchanges with deuterium oxide), 10.68 (br s, 1H, N^5-H, exchanges with deuterium oxide), 8.78 (s, 1H, H-2), 8.52 (s, 1H, H-4), 3.46 (s, 2H, H-7); ms: (70 eV, electron impact) m/z 178.10 (M^+, 100%).

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 46.98; H, 3.49; N, 31.05.

5,9-Dimethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**5**).

Sodium hydride (0.40 g, 16.8 mmoles of a 60% dispersion in mineral oil) was added in aliquots to a solution of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**4**, 1.2 g, 6.8 mmoles) in dimethylformamide (40 ml) at 0° and the mixture was stirred for twenty-five minutes. A solution of iodomethane (1.93 g, 13.6 mmoles) in dry ether (4 ml) was added dropwise and the reaction was allowed to proceed for one hour at 0° with stirring. Addition of water (400 ml), extraction with ethyl acetate (5 x 80 ml), drying the ethyl acetate fraction (magnesium sulfate) and removal of the solvent *in vacuo* afforded a yellow sodid. Recrystallizatiton from hexane:ethyl acetate (1:2, v/v) gave 5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**5**) as colorless crystals (0.784 g, 60%), mp 159-160°; ir (potassium bromide): ν 1695 (C=O) cm^{-1}; ^{1}H nmr (chloroform-d_1): δ 8.94 (s, 1H, H-2), 8.72 (s, 1H, H-4), 3.64 (d, J_{gem} = 15 Hz, 1H, C*H*H'), 3.56 (s, 3H, N^9-CH_3), 3.48 (s, 3H, N^5-CH_3), 3.28 (d, J_{gem} = 15 Hz, 1H, CH*H'*); ms: (70 eV, electron impact) m/z 206.25 (M^+, 100%).

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.59; H, 4.90; N, 26.82.

6,7,8,9-Tetrahydro-5,7,9-trimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**6**).

Sodium hydride (0.14 g, 5.8 mmoles of a 60% dispersion in mineral oil) was added in aliquots to a solution of 5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**5**, 0.82 g, 3.98 mmoles) in dimethylformamide (18 ml) at 0° with stirring and the mixture was stirred for an additional forty-five minutes at 0°. Iodomethane (0.565 g, 3.98 mmoles) in dry ether (2 ml) was added dropwise and the reaction was allowed to proceed at 0° for ninety minutes. Addition of water (200 ml), extraction with ethyl acetate (5 x 40 ml), drying the ethyl acetate extract (magnesium sulfate) and removal of the solvent *in vacuo* gave a residue. Preparative silica gel thin layer chromatography using ethyl acetate:methanol (20:1, v/v) as development solvent yielded 6,7,8,9-tetrahydro-5,7,9-trimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**6**, R_f 0.49, 0.57 g, 65%) as a solid which was recrystallized

from hexane:ethyl acetate (1:2, v/v) to provide colorless crystals, mp 145-146°; ir (potassium bromide): ν 1702, 1675 (C=O), 1562 (C=C) cm^{-1}; ^1H nmr (chloroform-d_1): δ 8.95 (s, 1H, H-2), 8.74 (s, 1H, H-4), 3.58 (s, 3H, N^9-CH_3), 3.50 (s, 3H, N^5-CH_3, irradiation of the N^5-CH_3 resonance provided a 14.9% nOe effect on the H-4 resonance), 3.15 (q, J = 6 Hz, 1H, H-7), 1.43 (d, J = 6 Hz, 3H, CH-CH_3); ms: (70 eV, electron impact) m/z 220.20 (M^+, 100%).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.39; H, 5.68; N, 25.59.

6,7,8,9-Tetrahydro-5,7,7,9-tetramethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**7**).

To an ice-cold of solution of 6,7,8,9-tetrahydro-5*H*-pyrimido-[4,5-*b*][1,4]diazepine-6,8-dione (**4**, 0.70 g, 3.93 mmoles) in dimethylformamide (35 ml) was added sodium hydride (0.40 g, 16.5 mmoles of a 60% dispersion in mineral oil) in aliquots during fifteen minutes at 0° with stirring. The reaction mixture was stirred at 0° for an additional twenty minutes, iodomethane (2.74 g, 16.02 mmoles) in dry ether (2 ml) was added and the reaction was allowed to proceed at 0° for ninety minutes. Water was added (350 ml), the mixture was extracted with ethyl acetate (8 x 50 ml), the combined ethyl acetate extracts were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give a yellow solid. Recrystallization from ethyl acetate:methanol (1:3, v/v) gave 6,7,8,9-tetrahydro-5,7,7,9-tetramethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-6,8-dione (**7**) as colorless crystals (0.42 g, 46%), mp 188-189°; ir (potassium bromide): ν 1682, 1652 (C=O), 1564 (C=C) cm^{-1}; ^1H nmr (chloroform-d_1): δ 8.90 (s, 1H, H-2), 8.64 (s, 1H, H-4), 3.61 (s, 3H, N^9-CH_3), 3.51 (s, 3H, N^5-CH_3), 1.60 and 1.0 (two s, 3H each, C-7 methyls); ms: (70 eV, electron impact) m/z 234.20 (M^+, 100%).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.07; H, 6.15; N, 23.80.

Acknowledgements.

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