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Pyrido[4,3-e]-1,4-diazepines and Pyrido[4,3-b]-1,5-benzodiazepines: Synthesis and Affinity to Brain Benzodiazepine Receptors

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Pyrido[4,3-*e*]-1,4-diazepines and fused tricyclic analogs thereof have been synthesized and tested for inhibition of benzodiazepine binding to receptors in various rat brain structures in comparison with standard drugs. Structure-affinity relationships are discussed.

Pyrido[4,3-e]-1,4-diazepine und Pyrido[4,3-b]-1,5-benzodiazepine: Synthese und Affinität zu Benzodiazepinrezeptoren im Gehirn.

Pyrido[4,3-e]-1,4-diazepine und ihre anellierten tricyclischen Analoga wurden synthetisiert und auf Affinität zu Benzodiazepinrezeptoren in verschiedenen Gehirnstrukturen von Ratten im Vergleich zu Standardarzneimitteln getestet. Struktur-Affinitäts-Beziehungen werden diskutiert.

We have recently reported on the synthesis of 4-chloro- and 4-amino-3-aroylpyridines via o-lithiation of 4-chloropyridine in the key step.[1] We describe now the application of the chloroketones **1a, b, c** for the synthesis of heterocycles with the pyrido[4,3-e]-1,4-diazepine ring system.

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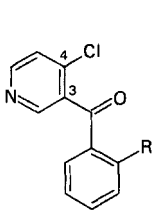
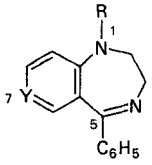
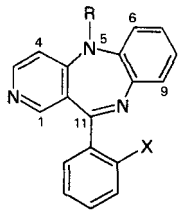


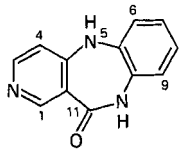
1a : R = H
1b : R = F
1c : R = Cl



2a : Y = N, R = H
2b : Y = N, R = CH_3
2c : Y = CCl, R = CH_3



3a : R = H, X = H
3b : R = H, X = F
3c : R = H, X = Cl
3d : R = $(CH_2)_3N(CH_3)_2$, X = H
3e : R = $(CH_2)_3N(CH_3)_2$, X = F



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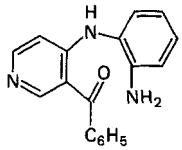

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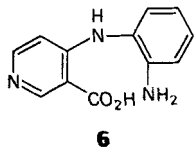

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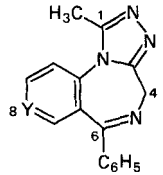
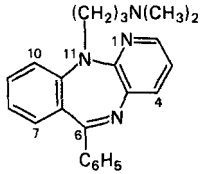


7 : Y = N
8 : Y = CCl



9 (AHR–9377)

The search in the synthesis of benzodiazepines and their annelated analogs led to the preparation of many new clinically useful derivatives of this type, including "heterodiazepines"[2-4]. Albeit the wide structural variety of heterocyclic inhibitors of binding to benzodiazepine receptors known todate, still the unique activity pattern of the benzo- and "hetero"-annelated 1,4-diazepines is to be stressed[5].

The great importance of an electron-withdrawing substitutent at C-7 of 1,4-benzodiazepines for biological activity[2], was confirmed by benzodiazepine receptors binding experiments[5]. However, the 7-aza analog of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam), containing the pyrido[4,3-e]-1,4-diazepine ring system, showed only weak diazepam-like CNS depressant properties *in vivo*[6, 7]. On the other hand 6-aza-1,4-benzodiazepines, containing a pyrido[3,2-e]-1,4-diazepine ring system, exhibit interesting anxiolytic and hypnotic activities[8, 9]. Furthermore, several 5H-dibenzo[b,e]-1,4-diazepine[10, 11], as well as 5H-pyrido[2,3-b]-1,4- and -1,5-benzodiazepine[12-14] tricyclic antidepressants have been prepared.

Chemistry

The 3-aroyl-4-chloropyridines **1a, b, c**, possessing two reactive electrophilic sites – C-4 and the carbonyl C-atom, react readily with bifunctional nucleophiles to yield cy-

clocondensation products. Thus, the 1H-pyrido[4,3-e]-1,4-diazeptine **2a** and the 5H-pyrido[4,3-b]-1,5-benzodiazepines **3a, b, c** were synthesized by condensation of the chloroketones **1a, b, c**[1] with ethylenediamine or with 1,2-phenylenediamine, respectively, in refluxing dimethylformamide. The 5,10-dihydro-11H-11-one derivative **4** of the novel pyrido[4,3-b]-1,5-benzodiazepine ring system was prepared by the analogous reaction of 4-chloropyridine-3-carboxylic acid with 1,2-phenylenediamine. Along with **3a** and **4**, the 4-(2-aminoanilino)pyridines **5** and **6** were isolated from the corresponding reactions of **1a** and of 4-chloropyridine-3-carboxylic acid with 1,2-phenylenediamine. This is to demonstrate, that C-4 in the two starting pyridine derivatives are more sensitive towards nucleophilic attack than the carbonyl centers adjacent to C-3[15].

Alkylation of **2a** and **3a, b** with H_3CI and 3-dimethylamino-1-propyl chloride in a solid/liquid two-phase system afforded **2b** and **3d, e**, respectively.

Binding to the Benzodiazepine Receptors

Compounds **2a, 3a, b, c, 4, 6, 2b** and **3d, e** were tested for their ability to displace [^{3}H] flunitrazepam from synaptosomal membranes of rat brain cortex, hippocampus and cerebellum. The recently described[16] 1-methyl-6-phenyl-4H-pyrido[3,4-f]-1,2,4-triazolo[4,3-a]-1,4-diazepine (**7**)[17] was evaluated in the same binding study. The data obtained (Table 1) were compared with those of the established drugs 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (medazepam; **2c**)[18] and 8-chloro-1-methyl-6-phenyl-4H-1,2,4-triazolo[4,3-a]-1,4-benzodiazepine (alprazolam; **8**)[19]. Data on a wide range of other standard drugs have been published elsewhere[5, 21].

Tab. 1: Inhibition of [^{3}H]Flunitrazepam Binding to Rat Brain Membranes[a]

Compound No.	IC_{50} (nM)		
	Brain Structure		
	Cortex	Hippocampus	Cerebellum
2a	> 100 000	> 100 000	> 100 000
3a	41 900	30 000	47 800
3b	31.5	35.2	29.9
3c	81.3	36.3	95.5
4	63 000	51 200	31 600
6	56 700	69 100	25 100
2b	51 200	33 800	30 100
3d	6 930	1 940	4 670
3e	4 660	4 360	2 180
7	2 560	2 730	1 840
2c	2 270	3 200	2 720
8	20.4	16.8	14.3

a) See Experimental Part.

The results obtained in this study indicate that the pyrido[4,3-e]-1,4-diazepines bind to the benzodiazepine receptors with reduced affinity as juxtaposed to their benzodiazepine analogs (compare compounds **2b** and **2c**, **7** and **8**, Table 1). This conclusion is consistent with earlier findings *in vivo*[6].

The pyridodiazepine **2a** is completely inactive even at 100 000 nM, the highest concentration tested. Annelation of additional rings to the '**a**' and '**b**' faces of the pyrido[4,3-e]-1,4-diazepine ring system yielded **7** and **3a**, respectively, with a moderate enhancement of binding affinity for the receptors. The replacement of the C-11 phenyl in **3a** by a carbonyl group as in the diazepinone **4** resulted in a decrease in affinity. The ring-opened compound **6** retained essentially the same binding affinity as the ring-closed form **4**, as already described for some 1,4-benzodiazepines[22].

Both a fluoro and a chloro substituent in the 2'-position enhance markedly the affinity for the benzodiazepine receptors (compare **3a** with **3b** and **3c**), the enhancement of a fluoro substituent being larger than that of a chloro substituent. Alkylation of **2a** at N-1 and of **3a** at N-5, leading to compounds **2b** and **3d**, respectively, results in an increase of binding affinity. Alkylation of **3b** to **3e** eliminates the effect of C-2' halogen substitution. The 6-aza isomer of **3d**, the 11-(3-dimethylaminopropyl)-6-phenyl-11H-pyrido[2,3-b]-1,4-benzodiazepine (AHR-9377; **9**)[12, 13], is completely inactive in a benzodiazepine receptors binding study *in vitro* (IC_{50} > 100 000 nM, using 1.5 nM [^{3}H]diazepam as a ligand)[23].

In addition, an interesting differential effect of the substituted pyrido[4,3-b]-1,5-benzodiazepines on receptors in hippocampus, cerebellum and cortex was detected. The 11-(2-chlorophenyl)- and 5-(3-dimethylaminopropyl)-11-phenyl substituted 5H-pyrido[4,3-b]-1,5-benzodiazepines (**3c** and **3d**, respectively) have a several times higher affinity for the benzodiazepine receptors in hippocampus than for those in cerebellum and cortex (compare the selectivity of various differential ligands, reported for benzodiazepine receptors in cerebellum versus hippocampus[21a] and cortex[21b]).

Experimental Part

Kieselgel 60 (0.063–0.200 mm; Merck) and Al_2O_3 S, neutral (activity grade 2; Riedel-de Haën) were used for column chromatography.

2,3-Dihydro-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine (**2a**)

2.54 g (0.01 mol) 3-benzoyl-4-chloropyridine-HCl (**1a** · HCl) and 15 ml ethylenediamine are heated to reflux for 1 h. The mixture is cooled, poured in 60 ml of a cold saturated aqueous Na_2CO_3 solution and extracted with 3 × 100 ml $CHCl_3$. The organic extracts are washed with 3 × 50 ml cold saturated aqueous Na_2CO_3 solution, dried over anhydrous Na_2SO_4 and evaporated i. vac. The oily residue is chromatographed on silica gel (100 g) and eluted with $CHCl_3$-hexane (1:1) to yield 1.61 g (72 %) of **2a**, m.p. 158–160°. – $C_{14}H_{13}N_3$ (223.3) Calc. C 75.3 H 5.87 N 18.8; Found C 75.0 H 6.25 N 18.8. – IR ($CHCl_3$): 3480, 3240, 3000, 1660, 1625, 1605, 1580 cm^{-1}. – ^{1}H-NMR ($CDCl_3$/HMDS, 100 MHz): δ (ppm) = 3.54 (dt, J = 4.0 Hz, 2H, H_2C-2), 4.00 (t, J = 4.0 Hz, 2H, H_2C-3), 5.80 (t, J = 4.0 Hz, 1H, HN-1, exchangeable with D_2O), 6.38 (d, J = 6.0 Hz, 1H, 9-H), 7.3 (m, 5H arom.), 7.94 (d, J = 6.0 Hz, 1H, 8-H), 8.00 (s, 1H, 6-H).

11-Aryl-5H-pyrido[4,3-b]-1,5-benzodiazepines **(3a, b, c)**

General procedure:
To 0.02 mol of the 3-aroyl-4-chloropyridine **1a, b, c** or its hydrochloride in 50 ml of anhydrous dimethylformamide 2.40 g (0.022 mol) 1,2-phenylenediamine is added and the mixture is refluxed for 3 h under argon. The solvent is removed i. vac. and the crude product purified by chromatography on silica gel (250 g), preactivated at 160° for 4 h. The product is eluted with benzene-ether (1:2).

11-Phenyl-5H-pyrido[4,3-b]-1,5-benzodiazepine **(3a)**: Orange crystals (chloroform/ether), m.p. 190–191°; Yield: 39 %. – $C_{18}H_{13}N_3$ (271.3) Calc. C 79.7 H 4.83 N 15.5; Found C 79.5 H 5.04 N 15.3. – IR ($CHCl_3$): 3410, 3000, 1650 (sh), 1630, 1610, 1585, 1490, 1470, 1410, 1300, 1110 cm^{-1}. – ^{1}H-NMR (d_6-DMSO, 250 MHz): δ (ppm) = 6.8 (m, 2H arom.), 7.0 (m, 2H arom.), 7.14 (dd, J = 6.9/2.2 Hz, 1H arom.), 7.4 (m, 3H arom.), 7.55 (d, J = 6.5 Hz, 2H arom.), 7.87 (s, 1H, HN-5, exchangeable with D_2O), 7.90 (s, 1H, 1-H), 8.32 (d, J = 5.4 Hz, 1H, 3-H). – MS(CI/i-C_4H_{10}): m/z = 272 (100 %, M + 1).
In addition, *4-(2-aminoanilino)-3-benzoylpyridine* **(5)** is isolated in 7 % yield by chromatography on silica gel using benzene-ether-MeOH (1:2:1) as eluent; oil: $C_{18}H_{15}N_3O$ (289.3) – MS (70 eV): m/z = 289 (2 %, $M^{+\cdot}$), 288 (1 %, M-H), 271 (15 %, M-H_2O), 270 (100 %, M-H_3O), 105 (2 %, C_6H_5CO), 77 (4 %, C_6H_5), 51 (2 %, C_4H_3). – ^{1}H-NMR ($CDCl_3$/HMDS, 100 MHz): δ (ppm) = 3.8 (br.s, 1H, HN, exchangeable with D_2O), 6.4–6.7 (m, 4H arom.), 7.4 (m, 5H arom.), 8.0–8.5 (m, 3H m.), 9.9 and 10.2 (2 br.s, 2H, H_2N, exchangeable with D_2O). – IR ($CHCl_3$): 3310 (br.), 3000, 1645, 1600, 1575, 1500, 1410, 1330 cm^{-1}.

11-(2-Fluorophenyl)-5H-pyrido[4,3-b]-1,5-benzodiazepine **(3b)**: Orange crystals (ether), m.p. 153–155° (dried i. vac. over P_2O_5); Yield: 52 %. – $C_{18}H_{12}FN_3$ (289.3) Calc. C 74.7 H 4.18 N 14.5; Found C 74.3 H 4.03 N 14.2. – ^{1}H-NMR (d_6-DMSO, 250 MHz): δ (ppm) = 6.8 (m, 2H arom.), 7.0 (m, 3H arom.), 7.3 (m, 2H arom.), 7.6 (m, 2H arom.), 7.69 (s, 1H, 1-H), 7.93 (s, 1H, HN-5), 8.22 (d, J = 4.8 Hz, 1H, 3-H).

11-(2-Clorophenyl)-5H-pyrido[4,3-b]-1,5-benzodiazepine **(3c)**: Orange crystals (benzene/ether or petroleum ether), m.p. 163–165° (dried i. vac. over P_2O_5); Yield: 78 %. – $C_{18}H_{12}ClN_3$ (305.8) Calc. C 70.7 H 3.96 N 13.7; Found C 70.7 H 4.31 N 13.4. – IR ($CHCl_3$): 3420, 3000, 1630, 1600, 1580, 1465, 1410, 1305, 1105 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 60 MHz): δ (ppm) = 5.7 (br.s, 1H, HN-5, exchangeable with D_2O), 6.5 (m, 2H arom.), 6.9–7.5 (m, 7H arom.), 7.68 (s, 1H, 1-H), 8.14 (d, J = 5.5 Hz, 1H, 3-H).

5,10-Dihydro-11H-pyrido[4,3-b]-1,5-benzodiazepin-11-one **(4)**: A mixture of 3.15 g (0.02 mol) 4-chloropyridine-3-carboxylic acid[24], 4.33 g (0.04 mol) 1,2-phenylenediamine and 50 ml anhydrous dimethylformamide is refluxed for 5 h. After cooling the mixture is diluted with 250 ml of cold water, the crude product is filtered off and purified by chromatography on silica gel (250 g) using $CHCl_3$-MeOH (10:1) as eluent. Yield: 1.82 g (43 %) of **4**, m.p. > 300°, decomp. (EtOH). – $C_{12}H_9N_3O$ (211.2) Calc. C 68.2 H 4.29; Found C 68.0 H 3.98. – IR (Nujol): 3400 (br), 1680, 1640, 1610, 1590, 1530 cm^{-1}. – ^{1}H-NMR (d_6-DMSO/HMDS, 80 MHz): δ (ppm) = 7.2–7.6 (m, 4H arom.), 7.70 (d, J = 7.0 Hz, 1H, 4-H), 8.44 (d, J = 7.0 Hz, 1H, 3-H), 8.90 (s, 1H, 1-H), 10.46 (s, 1H, HN-5, exchangeable with D_2O), 11.50 (s, 1H, HN-10, exchangeable with D_2O). – MS (70 eV): m/z = 211 (100 %, $M^{+\cdot}$), 183 (2 %, M-CO), 182 (5 %, 183-H), 156 (3 %, 183-HCN), 155 (3 %, 182-HCN).
In addition, *4-(2-aminoanilino)pyridine-3-carboxylic acid* **(6)** is isolated in 13 % yield by chromatography on silica gel using $CHCl_3$-MeOH (1:1) as eluent; m.p. 246–247° (EtOH), $C_{12}H_{11}N_3O_2$ (229.2). – MS (70 eV): m/z = 229 (15 %, $M^{+\cdot}$), 211 (100 %, M-H_2O), 183 (3 %), 182 (4 %), 156 (3 %), 155 (3 %). – IR (Nujol): 3410, 3330, 3300–3200 (br.), 2700–2300 (v.br.), 1650, 1550, 1510, 1490, 1370, 1280 cm^{-1}.

2,3-Dihydro-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine **(2b)**: To a stirred suspension of 420 mg of crushed 85.0 % KOH pellets in 2 ml of dry dimethyl sulfoxide at ambient temp. 335 mg (1.5 mmol) pyridodiazepine **2a** is added. After 45 min 0.20 ml (3.2 mmol) of H_3CI are added and stirring is continued for 30 min. The mixture is diluted with 5 ml of cold water and extracted with 5 × 10 ml ether. The organic extracts are dried over anhydrous Na_2SO_4 and concentrated i. vac. The residue is chromatographed on

Al_2O_3 (50 g) eluting with hexane-chloroform (2:1) to yield 193 mg (54 %) of **2b**, m.p. 128–130° (ether/heptane). – $C_{15}H_{15}N_3$ (237.3) Calc. C 75.9 H 6.37 N 17.7; Found C 75.9 H 6.32 N 17.7. – ^{1}H-NMR (d_6-DMSO, 250 MHz): δ (ppm) = 2.84 (s, 3H, H_3CN-1), 3.69 (d, J = 4.6 Hz, 2H, H_2C-2), 3.85 (d, J = 3.0 Hz, 2H, H_2C-3), 6.83 (d, J = 5.9 Hz, 1H, 9-H), 7.41 (s, 5H arom.), 7.82 (s, 1H, 6-H), 8.22 (d, J = 5.7 Hz, 1H, 8-H).

11-Aryl-N,N-dimethyl-5H-pyrido[4,3-b]-1,5-benzodiazepine-5-propanamines **(3d, e)**

General procedure:

To a stirred suspension of 1.25 g of crushed 85.0 % KOH pellets in 3 ml of dry dimethyl sulfoxide 1.25 mmol of the pyridobenzodiazepine **3a, b** is added. The mixture is stirred vigorously at 55° for 1 h and then cooled to ambient temp. A solution of 395 mg (2.5 mmol) of 3-dimethylamino-1-propyl chloride-HCl in 3 ml of dimethyl sulfoxide is added dropwise and 210 mg (1.25 mmol) of KI is added next. The mixture is stirred at 75° for an additional 2.5 h, then cooled to ambient temp. and diluted with 15 ml of cold water. The mixture is extracted with 5 × 20 ml $CHCl_3$. The organic extracts are washed with 2 × 10 ml of saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 and concentrated i. vac. The residue is chromatographed on Al_2O_3 or silica gel (50 g) and the product is eluted with hexane-chloroform (1:1) or with benzene-ether-MeOH (1:2:2), respectively.

11-Phenyl-N,N-dimethyl-5H-pyrido[4,3-b]-1,5-benzodiazepine-5-propanamine **(3d)**: yellow crystals (ether), m.p. 134–135°; Yield: 50 %. – $C_{23}H_{24}N_4$ (356.5) Calc. C 77.5 H 6.79 N 15.7; Found C 77.4 H 6.68 N 15.6. – ^{1}H-NMR (d_6-DMSO, 250 MHz): δ (ppm) = 1.7 (m, 2H, $(CH_3)_2NCH_2\underline{CH_2}CH_2N$-5), 1.97 (s, 6H, $(\underline{CH_3})_2N$), 2.2 (m, 2H, $(CH_3)_2NCH_2\underline{CH_2}CH_2N$-5), 3.7 (m, 2H, $(CH_3)_2NCH_2CH_2\underline{CH_2}N$-5), 7.05–7.25 (m, 5 H arom.), 7.5 (m, 3H arom.), 7.64 (d, J = 6.4 Hz, 2H arom.), 8.06 (s, 1H, 1-H), 8.54 (d, J = 5.5 Hz, 1H, 3-H).

11-(2-Fluorophenyl)-N,N-dimethyl-5H-pyrido[4,3-b]-1,5-benzodiazepine-5-propanamine **(3e)**: Orange crystals (ether), m.p. 108–111° (dried i. vac. over P_2O_5); Yield: 46 %. This product is highly moisture-sensitive. – $C_{23}H_{23}FN_4$ (374.5) Calc. C 73.8 H 6.19 N 15.0, Found C 74.0 H 6.54 N 14.7. – ^{1}H-NMR (d_6-DMSO, 250 MHz): δ (ppm) = 1.7 (m, 2H, $(CH_3)_2NCH_2\underline{CH_2}CH_2N$-5), 2.02 (s, 6H, $(\underline{CH_3})_2N$), 2.3 (m, 2H, $(CH_3)_2NCH_2\underline{CH_2}CH_2N$-5), 3.7 (m, 2H, $(CH_3)_2NCH_2CH_2\underline{CH_2}N$-5), 7.05–7.80 (m, 9H arom.), 7.94(s, 1H, 1-H), 8.49 (d, J = 5.5 Hz, 1H, 3-H). – MS (70 eV): m/z = 374 (3 %, $M^{+\cdot}$), 316 (12 %, $M\text{-}CH_2N(CH_3)_2$), 303 (4 %), 58 (100 %, $CH_2 = N(CH_3)_2$).

Measurement of [^{3}H]flunitrazepam binding:

Wistar male rats weighing 180–200 g were used in all studies. Binding to the benzodiazepine receptors was accomplished according to[25] using synaptosomal membranes of rat brain cortex, hippocampus and cerebellum. The final concentration of [^{3}H]flunitrazepam (Amersham, England; specific activity 84 Ci/mmol) was 1.5 nM. Nonspecific binding was determined from parallel experiments carried out in the presence of 3 μM diazepam. Test compounds were dissolved in EtOH and serial dilutions were added to the binding assay to estimate the concentrations required for 50 % inhibition of specific [^{3}H]flunitrazepam binding (IC_{50}). The radioactivity of the samples was determined after the addition of 5 ml of the scintillation cocktail: 33 % Triton × 100, 0.8 % PPO and 0.01 % POPOP in toluene and registered using a Beckman LS 9800 scintillation counter.

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