Quinazolines and 1,4-benzodiazepines. XCIV (1). Pyrazino[1,2-*a*][1,4]benzodiazepines

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A series of pyrazino[1,2-*a*][1,4]benzodiazepines were prepared by acylating the primary amino group of an α-amino-1,4-benzodiazepine-2-ylideneacetic acid ester (**1**) with α-chloroacyl chlorides followed by cyclodehydrohalogenation with triethylamine in dimethylformamide. Some pharmacological data for CNS-activity are discussed.

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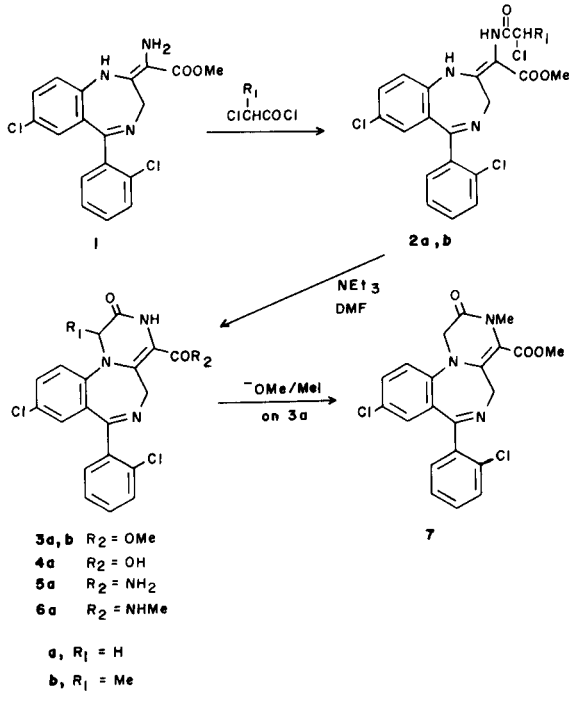
The benzodiazepine **1** has been a key intermediate for the synthesis of various imidazo[1,5-*a*][1,4]benzodiazepines (2). The functionality of this compound is also suitable for the preparation of other 1,2-fused benzodiazepines. In this note we described the synthesis of new pyrazino[1,2-*a*][1,4]benzodiazepines from **1**. The primary amino group of **1** was acylated with 2-chloroacyl chlorides in boiling methylene chloride to give the acyl derivatives **2**. The stereochemistry of these compounds is uncertain, but the subsequent ring closure suggests that the structure is as shown in **2**. Dehydrohalogenation with cyclization of **2** to **3** was achieved by heating **2** in dimethylformamide in the presence of triethylamine. The ester **3a** was hydrolyzed to the corresponding acid **4a** by sodium hydroxide in methanol/water. Compound **4a** was converted *via* the intermediate acid chloride in the primary and secondary amides **5a** and **6a**, respectively. Methylation of **3a** with sodium methoxide and methyl iodide in dimethylformamide gave the *N*-methyl derivative **7**.

Ring closure of the 3-chloropropionamide **8** under similar conditions did not lead to diazepinobenzodiazepine **9**, but to a mixture of the pyrrolidinone **11** and the acrylamide **10**. The latter was also prepared by heating **1** with acrylic acid chloride in boiling methylene chloride. Since **10** did not convert to **11** under the ring closure conditions, it is not an intermediate in the formation of the pyrrolidinone.

Biological Data.

The compounds were tested orally in mice for the CNS effects of benzodiazepines according to previously described procedures (3). The ED_{50}'s of the pentamethylentetrazole antagonism test are listed in table I. The ester **3a**, the acid **4a** and the amides **5a** and **6a** approach the activity of diazepam in this test. In contrast to other benzodiazepines bearing a carboxy group, the acid **4a** showed a relatively high potency. This may de due to a rapid biotransformation to a less polar metabolite which

Scheme I



Scheme II

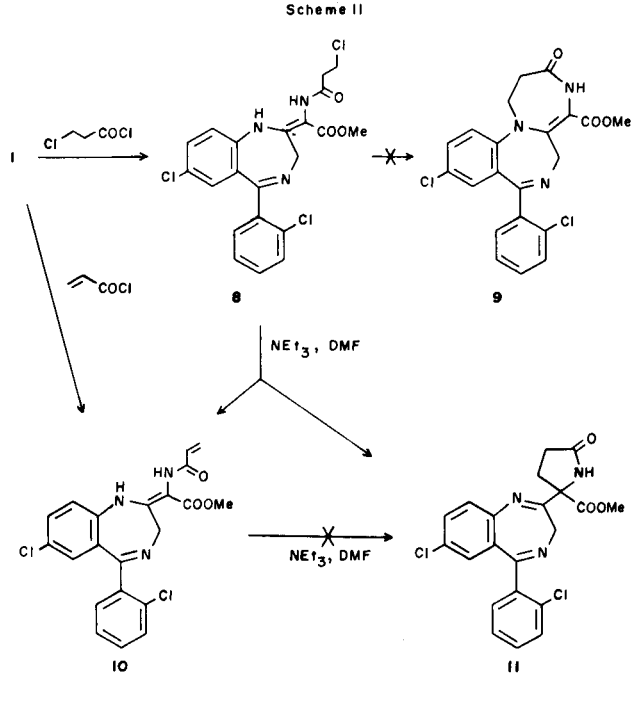


Table I

Compound	Pentamethylentetrazole antagonism ED_{50} mg/kg p.o.
Diazepam (a)	1.4
3a	4.3
3b	12.0
4a	3.7
5a	2.0
6a	1.6
7	18.0
10	24.0
11	5.1

(a) Except for compound **6a** (LD_{50} = 900 mg/kg p.o.) the LD_{50} for all compounds was greater than 1000 mg/kg p.o.

would better penetrate the blood-brain barrier. Introduction of a methyl group in position 1 and 3 of compound **3a** did not improve the activity. The pyrrolidine derivative **11** was still fairly potent.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrometer. The nmr spectra were recorded with a Varian T-60 instrument with tetramethylsilane as the internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Merck silica gel (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

7-Chloro-α-(2-chloroacetylamino)-5-(2-chlorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene Acetic Acid Methyl Ester (**2a**).

A mixture of 30 g (0.071 mole) of α-amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene acetic acid methyl ester ethanolate, (**1**) (2), 15 ml of chloroacetyl chloride and 1500 ml of methylene chloride was heated to reflux for 5 minutes. The reaction mixture was washed with saturated aqueous sodium bicarbonate, dried and evaporated. Crystallization of the residue from ether gave 31.8 g (98%) of product with mp 187-189°. The analytical sample was recrystallized from methylene chloride/ether/methanol to give off-white crystals with mp 192-194° dec; nmr (deuteriochloroform): δ 3.75 (s, 3, OCH_3) 4.17 (s, 2, CH_2Cl) 4.43 (s, 2, C_3-H) 6.9-7.8 (m, 8, aromatic H, NH) 11.15 ppm (broad s, 1, NH).

Anal. Calcd. for $C_{20}H_{16}Cl_3N_3O_3$: C, 53.06; H, 3.56; N, 9.78. Found: C, 53.12; H, 3.60; N, 9.43.

9-Chloro-7-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydropyrazino[1,2-*a*][1,4]-benzodiazepine-4-carboxylic Acid Methyl Ester (**3a**).

A mixture of 30 g (0.066 mole) of **2a**, 60 ml of triethylamine and 1200 ml of dry dimethylformamide was heated to reflux for 5 minutes. The solvents were removed under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ethanol yielded 20.4 g (74%) of yellow crystals with mp 204-207°. The analytical sample was recrystallized from ethanol, mp unchanged; uv: λ max 217 nm (ε 34200) sh *ca.* 250 (14600) 341 (22400); ir ($CHCl_3$) 3410, 3390 cm^{-1} (NH) 1685 ($COOCH_3$, CO); nmr (deuteriochloroform) δ 3.86 (s, 3, OCH_3), 4.32 (s, 2, CH_2), 5.1 (broad s, 2, C_5-H), 6.95 (d, 1, J = 2 Hz, C_8-H) 7.15 (d, 1, J = 9 Hz, $C_{11}-H$) 7.2-7.7 (m, 5, aromatic H) 7.8 (broad s, 1, NH).

Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O_3$: C, 57.71; H, 3.63; N, 10.09. Found: C, 57.85; H, 3.73; N, 10.32.

9-Chloro-7-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydropyrazino-[1,2-*a*]1,4-benzodiazepine-4-carboxylic Acid Methyl Ester (**3b**).

A solution of 10 g (0.0236 mole) of α-amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene acetic acid methyl ester ethanolate, (**1**) (2) and 5 ml (0.05 mole) of 2-chloropropionyl chloride in 500 ml of methylene chloride was stirred and refluxed under a nitrogen atmosphere for 5 minutes. The solution was cooled, washed with 300 ml of saturated aqueous sodium bicarbonate containing 10 ml of triethylamine and then dried and evaporated. A solution of this residue and 20 ml of triethylamine in 300 ml of dimethylformamide was stirred and refluxed under a nitrogen atmosphere for 2 hours and then evaporated to dryness. This residue was dissolved in 300 ml of methylene chloride, washed with saturated sodium bicarbonate solution, dried and evaporated. This residue was chromatographed over a 30 fold amount of silica gel using methylene chloride/ethyl acetate 1:1 (v/v). The fractions containing product were combined and evaporated. Crystallization from 2-propanol/ether yielded 1.9 g (19%) of crystals with mp 211-213°. Recrystallization for analysis from ethyl acetate/hexane gave off-white crystals with mp 213-215° nmr (DMSO): δ 1.32 (d, 3, J = 6.5 Hz, CH_3) 2.07 (s, 3, OCH_3), 4.4 (broad s, 1) and 5.4 (broad s, 1) (broad AB-system, C_5-H), 4.55 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.85 (d, 1, J = 1.5 Hz, C_8-H), 7.3-7.6 (m, 6 aromatic H), 9.3 (broad s, 1, NH).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O_3$: C, 58.62; H, 3.98; N, 9.77. Found: C, 58.41; H, 4.13; N, 9.68.

9-Chloro-7-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydropyrazino[1,2-*a*][1,4]-benzodiazepine-4-carboxylic Acid (**4a**).

A mixture of 8.32 g (0.02 mole) of **3a**, 5.6 g (0.1 mole) of potassium hydroxide 400 ml of methanol and 40 ml of water was heated to reflux for 2.5 hours under an atmosphere of nitrogen. The methanol was removed under reduced pressure and the residue was diluted with 1 ℓ of water and acidified with glacial acetic acid. After stirring for 10 minutes the precipitated crystalline acid was filtered off, washed with water an sucked dry. Crystallization from tetrahydrofuran/ethanol/water gave 6.4 g (79%) if light yellow product with mp, 230-235° dec; uv: λ max 217 nm (ε 32500) sh *ca.* 250 (13400) 337 (18200).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O_3$: C, 56.74; H, 3.26; N, 10.45. Found: C, 56.83; H, 3.54; N, 10.14.

9-Chloro-7-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydropyrazino[1,2-*a*][1,4]-benzodiazepine-4-carboxamide ethanolate (**5a**).

A mixture of 4 g of (0.01 mole) of **4a** and 100 ml of thionyl chloride was stirred at room temperature for 2 minutes. The reagent was evaporated under reduced pressure and the residue was slurried in 200 ml of tetrahydrofuran. A solution of ammonia in tetrahydrofuran was added until the reaction mixture was alkaline. It was diluted with methylene chloride and washed with aqueous sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was crystallized from tetrahydrofuran/ethanol to yield 2.7 g (60%) of light yellow crystals with mp 230-240° dec. For analysis the product was recrystallized from the same solvents; mp unchanged; nmr (d-DMSO): δ 4.16 (s, 2, CH_2) 4.83 (broad s, 2, C_5-H) 6.73 (d, 1, J = 2 Hz C_8-H), 7.1-7.7 (m, 8, aromatic H and NH_2), 9.45 ppm (broad s, 1, NH), ethanol was detected in molar amounts.

Anal. Calcd. for $C_{19}H_{14}Cl_2N_4O_2 \cdot C_2H_6O$: C, 56.39; H, 4.51; N, 12.53. Found: C, 56.33; H, 4.52; N, 12.26.

9-Chloro-7-(2-chlorophenyl)-*N*-methyl-2-oxo-1,2,3,5-tetrahydropyrazino-[1,2-*a*][1,4]benzodiazepine-4-carboxamide (**6a**).

Reaction of 4 g of **4a** with thionyl chloride followed by methylamine

gave similarly 1.8 g (43%) of **6a** which was recrystallized from tetrahydrofuran/ethanol for analysis, mp 249-252°; nmr (d-DMSO): δ 2.72 (d, 3, J = 5 Hz, $NHCH_3$), 4.16 (s, 2, CH_2), 4.76 (s, 2, C_5-H), 6.77 (d, 1, J = 2 Hz, C_8-H) 7.1-8.0 (m, 7, aromatic H, $NHCH_3$), 9.45 (broad s, 1, NH).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_4O_2$: C, 57.84; H, 3.88; N, 13.49. Found: C, 57.65; H, 4.04; N, 13.53.

9-Chloro-7-(2-chlorophenyl)-3-methyl-2-oxo-1,2,3,5-tetrahydropyrazino-[1,2-*a*][1,4]benzodiazepine-4-carboxylic Acid Methyl Ester (**7**).

Sodium methoxide, 1.56 g (0.03 mole) was added to a stirred solution of 4.16 g (0.01 mole) of **3a** in 150 ml of dry dimethylformamide. After stirring for 15 minutes at room temperature 2.4 ml (5.6 g or 0.04 mole) of methyl iodide was added and stirring was continued for 15 minutes. The reaction mixture was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried and evaporated. Crystallization of the residue from ethyl acetate gave 2.7 g (63%) of product with mp 183-185°. For analysis it was recrystallized from methylene chloride/ether to leave yellow crystals with mp 184-186°; uv: λ max 216 nm (ε 36900) sh 250 (13600) max 327 (19300); ir (chloroform): infl 1705 ($COOCH_3$) 1670 (CO) 1620 (C=N); nmr (deuteriochloroform): 3.16 (s, 3, NCH_3), 3.9 (s, 3, OCH_3), 4.27 (s, 2, CH_2), 4.87 (s, 2, C_5-H), 6.95 (d, 1, J = 2 Hz, C_8-H), 7.05 (d, 1, J = 9Hz, $C_{11}-H$), 7.2-7.6 ppm (m, 5, aromatic H).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O_3$: C, 58.62; H, 3.98; N, 9.77. Found: C, 58.79; H, 4.02; N, 9.57.

7-Chloro-α-{[(2-chloroethyl)carbonyl]amino}-5-(2-chlorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylideneacetic Acid Methyl Ester (**8**).

A mixture of 8.44 g (0.02 mole) of α-amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylideneacetic acid methyl ester ethanolate (**1**) (2), 200 ml of methylene chloride and 8 ml of 3-chloropropionyl chloride was heated to reflux for 5 minutes. The solution was washed well with 10% aqueous sodium carbonate solution containing triethylamine. The organic phase was dried and evaporated. Crystallization of the residue from ethyl acetate/ether gave 5.1 g (54%) of yellow crystals with mp 176-179° dec. The analytical sample was recrystallized from methylene chloride/ether; nmr (deuteriochloroform): δ 2.76 (t, 2, J = 6 Hz, $COCH_2$), 3.7 (s, 3, OCH_3), 3.85 (t, 2, J = 6 Hz, CH_2Cl), 4.48 (broad s, 2, C_3-H), 6.8-7.8 (m, 8, aromatic H, NH), 11.0 (broad s, 1, NH).

Anal. Calcd. for $C_{21}H_{18}Cl_{N3}O_3$: C, 54.04; H, 3.89; N, 9.00. Found: C, 54.00; H, 3.91; N, 8.92.

7-Chloro-5-(2-chlorophenyl)-2,3-dihydro-α-[(1-oxo-2-propenyl)amino]-1*H*-1,4-benzodiazepin-2-ylideneacetic Acid Methyl Ester (**10**).

A mixture of 4.22 g (0.01 mole) of α-amino-7-chloro-5-(2-chlorophenyl)-1,2-dihydro-1*H*-1,4-benzodiazepin-2-ylideneacetic acid methyl ester ethanolate (**1**) (2), 250 ml of methylene chloride and 2 ml of acryloyl chloride was heated to reflux for 5 minutes and was then washed with 10% aqueous sodium carbonate solution containing triethylamine. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ethyl acetate/ether yielded 3.9 g (90%) crude product with mp 188-192°. For analysis this material was passed over a plug of silica gel using ethyl acetate. Recrystallization from ethyl acetate/ether gave colorless product with mp 203-206°; nmr (DMSO): δ 3.64 (s, 3, OCH_3), 4.43 (broad s, 2, C_3-H), 5.4-6.5 (m, 3, olefinic H), 6.78 (d, 1, J = 2 Hz, C_6-H), 7.2-7.6 (m, 6 aromatic H), 9.15 (s, 1, NH), 10.9 (s, 1, NH).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O_3$: C, 58.62; H, 3.98; N, 9.77. Found: C, 58.64; H, 3.94; N, 9.63.

2-[7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]-5-oxo-2-pyrrolidinecarboxylic Acid Methyl Ester (**11**).

A mixture of 5 g of **8**, 10 ml of triethylamine and 100 ml of dimethylformamide was heated to reflux under an atmosphere of nitrogen for 10 minutes. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was dried and evaporated. The residue was chromatographed over 250 g of silica gel using methylene chloride/ethyl acetate 7:3 (v/v) for elution of the less polar product. Crystallization from ethyl acetate/ether gave 2.6 g of compound **10** with mp 203-206°. The more polar component was eluted with ethyl acetate and crystallized from ethyl acetate/ether to yield 1.7 g (37%) of colorless crtystals with mp 209-212°. The analytical sample was recrystallized from ethyl acetate/hexane, mp 210-212° dec; nmr (deuteriochloroform): δ 2.2-3.1 (m, 4, CH_2), 3.8 (s, 3, OCH_3), 4.1 (broad AB-system, 2, J = 12 Hz, C_3-H), 6.9 (broad s, 1, NH), 7.0-7.6 (m, 7, aromatic H); uv: λ max 219 nm (ε 41700) sh 240 (21800) 295 (4640) sh 317 (4000); ir (chloroform) 3425 cm^{-1} (NH), 1745 (COOMe) 1710 (CON).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O_3$: C, 58.62; H, 3.98; N, 9.77. Found: C, 58.62; H, 3.86; N, 9.68.

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