Heterocycles with a Benzothiadiazepine Moiety. 2. Synthesis of 2-Methyl-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo-[1,2-*b*][1,2,5]benzothiadiazepine 10,10-Dioxide (Tiaaptazepine)

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The synthesis of 2-methyl-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 10,10-dioxide (tiaaptazepine), a novel tetracyclic structure strictly related to antidepressant aptazepine, is described starting from 1-(2-aminobenzenesulfonyl)pyrrole. Reaction of this compound with ethyl glyoxylate hemiacetal gave 10,11-dihydro-11-ethoxycarbonylpyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide, which was reacted with bromoacetyl bromide and then with benzylamine to afford 2-benzyl-1,4-dioxo-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 10,10-dioxide. Lithium aluminum hydride-sulfuric acid reduction of this derivative followed by debenzylation and subsequent methylation afforded the title compound.

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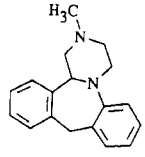
Studies on tetracyclic analogues of mianserin **1** have led to the discovery of aptazepine **2**, an antidepressant drug devoid of sedative activity which contains the pyrrole ring as a typical moiety. Other mianserin-like antidepressant agents which were found active in pharmacological studies are 6-azamianserin **3** and tianeptine **4** [1].



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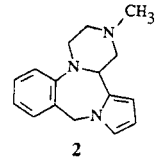

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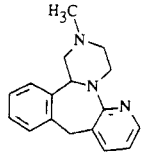

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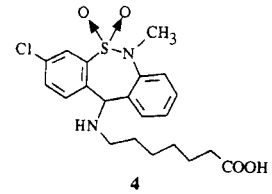

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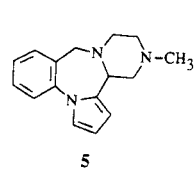
As new approaches to pyrrole-containing polycyclic rings [2-6] we recently reported the synthesis of some novel tetracyclic derivatives strictly related to aptazepine, namely isoaptazepine **5** [7-9], 10-methyl-10-azaaptazepine **6** [10,11] and two pyrazole analogues of isoaptazepine [12]. Pursuing our search on this approach we now describe the preparation of 2-methyl-1,3,4,14b-tetrahydro-2*H*-pyrazino-[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 10,10-dioxide (**7**) (tiaaptazepine), a new potential antidepressant agent which shares some chemical features with derivatives **2** and **4**.

The synthetic pathway leading to derivative **7** is depicted in Scheme 1.

Reaction of 1-(2-aminobenzenesulfonyl)pyrrole [13] with ethyl glyoxylate hemiacetal *via* a Pictet-Spengler type condensation [14] led to the ethyl ester of 11-carboxy-10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide **8**, which was treated with bromoacetyl bromide in the presence of sodium bicarbonate to afford 10-bromoacetyl-11-ethoxycarbonyl-10,11-dihydropyrrolo[1,2-*b*][1,2,5]-benzothiadiazepine 5,5-dioxide **9**. Treatment of **9** with benzylamine followed by thermal cyclization of the benzylaminoacetyl intermediate **10** furnished the dioxopiperazinyl derivative **11**. Reduction of the last compound with lithium aluminum hydride-sulfuric acid mixture gave 2-benzyl-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo-[1,2-*b*][1,2,5]benzothiadiazepine 10,10-dioxide **12**, which was debenzylated to **13** by treatment with hydrogen in the presence of 10% palladium on charcoal as the catalyst.

Methylation of **13** was achieved with formaldehyde in the presence of hydrogen to furnish the required derivative **7**.



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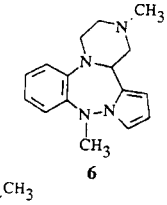

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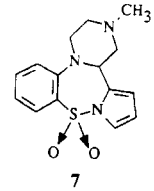

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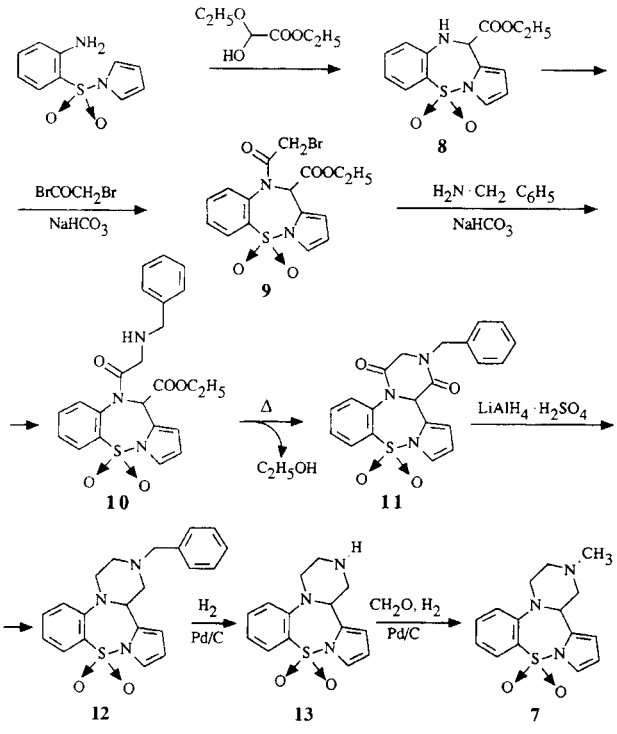
EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. The pmr spectra were recorded in deuteriochloroform with a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as internal standard. Column chromatographies were performed on alumina Merck (70-230 mesh)

Scheme 1



and silica gel Merck (70-230 mesh). Aluminum oxide/tlc-cards Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator 254 nm) and Silica gel/tlc-cards Fluka (silica gel precoated aluminum cards with fluorescent indicator 254 nm) were used for thin layer chromatography. Developed plates were visualized by uv light. Organic solutions were dried over anhydrous sodium sulfate. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator (Büchi) operating at reduced pressure (approximately 20 bar). Elemental analyses were performed by laboratories of Professor A. Pietrogrande, University of Padova, Italy.

11-Ethoxycarbonyl-10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-Dioxide (**8**).

A solution of 1-(2-aminobenzenesulfonyl)pyrrole (22.22 g, 0.10 mole) and ethoxy hemiacetal of ethyl glyoxylate (22.22 g, 0.15 mole) in absolute ethanol (500 ml) was heated at reflux under a nitrogen stream for 65 hours. Evaporation of the solvent gave a residue which was purified on an alumina column eluting with chloroform. The first fractions were collected and evaporated to give 28.8 g of **8** (94%) as an oil which solidified on standing, mp 121-122° (after crystallization from benzene/cyclohexane); ir (nujol): ν 1720 (CO), 3360 cm^{-1} (NH); pmr: δ 1.33 (t, 3H, $COOCH_2CH_3$), 4.40 (q, 2H, $COOCH_2CH_3$), 5.60-5.81 (s broad, 1H, NH, disappeared on treatment with deuterium oxide), 5.93 (m, 1H, pyrrole), 6.13-6.30 (m, 2H, pyrrole and CH), 6.58-6.86 (m, 2H, benzene), 7.20-7.43 (m, 2H, pyrrole and benzene), 7.73-7.93 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: C, 54.88; H, 4.60; N, 9.14; S, 10.46. Found: C, 54.89; H, 4.65; N, 9.16; S, 10.40.

10-Bromoacetyl-11-ethoxycarbonyl-10,11-dihydropyrrolo[1,2-*b*]-[1,2,5]benzothiadiazepine 5,5-Dioxide (**9**).

A solution of bromoacetyl bromide (4.24 g, 0.021 mole) in 1-bromo-3-chloropropane (20 ml) was added dropwise into an ice-cooled mixture of **8** (6.12 g, 0.02 mole) and sodium hydrogen carbonate (1.85 g, 0.22 mole) in the same solvent (100 ml). The reaction mixture was refluxed overnight, then cooled at room temperature, filtered, and the solvent was evaporated. The crude residue was dissolved in chloroform, dried and after concentration to a small volume purified on alumina column eluting with the same solvent. The first fractions were discarded. Central eluates were collected and evaporated to give 5.3 g of compound **9** (62%), mp 155-157° (after crystallization from benzene/cyclohexane); ir (nujol): ν 1675 (CO amide), 1730 cm^{-1} (CO ester); pmr: δ 1.33 (t, 3H, $COOCH_2CH_3$), 3.70 and 3.85 (2d, 2H, ABq, J = 12 Hz, methylene), 4.36 (q, 2H, $COOCH_2CH_3$), 6.16 (m, 2H, pyrrole), 6.40 (s, 1H, CH), 7.21-8.06 ppm (m, 5H, pyrrole and benzene).

Anal. Calcd. for $C_{16}H_{15}BrN_2O_5S$: C, 44.97; H, 3.53; Br, 18.70; N, 6.55; S, 7.50. Found: C, 45.12; H, 3.72; Br, 18.64; N, 6.61; S, 7.55.

10-Benzylaminoacetyl-11-ethoxycarbonyl-10,11-dihydropyrrolo-[1,2-*b*][1,2,5]benzothiadiazepine 5,5-Dioxide (**10**).

A solution of benzylamine (0.33 g, 0.0023 mole) in dry tetrahydrofuran (5 ml) was added dropwise into a mixture of **9** (1.00 g, 0.0023 mole) and sodium hydrogen carbonate (0.20 g, 0.0024 mole) in the same solvent (20 ml), then the reaction was refluxed for 7 hours. The salt which formed was filtered and the solvent was evaporated. The oily residue was dissolved in chloroform and dried. After concentration to a small volume the crude product was purified on a silica gel column eluting with the same solvent. The first fractions were discarded. The central eluates were collected and evaporated to give 0.63 g of **10** (61%) as a thick oil; ir (neat): ν 1660 (CO amide), 1730 (CO ester), 3320 cm^{-1} (NH); pmr: δ 1.33 (t, 3H, $COOCH_2CH_3$), 2.13 (s, 1H, NH, disappeared on treatment with deuterium oxide), 2.97 and 3.35 (2d, 2H, ABq, J = 16.5 Hz, methylene), 3.62 and 3.67 (2d, 2H, ABq, J = 13.5 Hz, methylene), 4.35 (q, 2H, $COOCH_2CH_3$), 6.11 (m, 2H, pyrrole), 6.48 (s, 1H, CH), 7.11-7.66 (m, 9H, pyrrole and benzene), 7.80-8.00 ppm (m, 1H, benzene).

2-Benzyl-1,4-dioxo-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 10,10-Dioxide (**11**).

A solution of **10** (1.00 g, 0.0022 mole) in toluene (30 ml) was refluxed overnight. After evaporation of the solvent, the residue was purified on silica gel column eluting with chloroform. Removal of the solvent from the central eluates gave 0.76 g of **11** (85%), mp 161-163° (after crystallization from toluene/ligroin); ir (nujol): ν 1660 cm^{-1} (CO); pmr: δ 4.05 (s, 2H, methylene), 4.69 and 5.00 (2d, 2H, ABq, J = 15 Hz, methylene), 5.61 (s, 1H, CH), 6.26 (m, 1H, pyrrole), 6.50 (m, 1H, pyrrole), 7.28-7.88 (m, 9H, pyrrole and benzene), 8.01-8.20 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{21}H_{17}N_3O_4S$: C, 61.90; H, 4.20; N, 10.31; S, 7.89. Found: C, 61.81; H, 4.28; N, 10.33; S, 7.98.

2-Benzyl-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*]-[1,2,5]benzothiadiazepine 10,10-Dioxide (**12**).

Concentrated sulfuric acid (0.77 ml) was carefully added dropwise over a period of 4 minutes into an ice-cooled suspension of lithium aluminium hydride (1.19 g, 0.030 mole) in dry tetrahydrofuran (25 ml). The mixture was stirred at room temperature for 30 minutes. A solution of the diketopiperazine **11** (1.00 g, 0.0025 mole) in the same solvent (17 ml) was slowly added dropwise, then the reaction was kept at room temperature for 2 hours. The mixture was cooled to −15° and quenched by slow dropwise addition of 2*N* sodium hydroxide (9.4 ml). The solid was removed by filtration, washed with tetrahydrofuran and the combined filtrates were concentrated to a small volume. After extraction with chloroform, the organic solution was washed with brine, dried and evaporated to give a residue which was chromatographed on an alumina column eluting with chloroform/petroleum ether 1:1. The first fractions were discarded. The central eluates were collected and evaporated to give 0.46 g of **12** (50%), mp 156-158° (after crystallization from toluene/ligroin); pmr: δ 2.36-3.00 (m, 4H, methylenes), 3.40-3.68 [4H, overlapped signals, m, s, (3.60), methylenes], 4.86 (t, 1H, CH), 6.06-6.25 (m, 2H, pyrrole), 6.80-7.56 (m, 9H, pyrrole and benzene), 7.73-7.90 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{21}H_{21}N_3O_2S$: C, 66.46; H, 5.57; N, 11.07; S, 8.45. Found: C, 66.55; H, 5.45; N, 10.94; S, 8.60.

1,3,4,14b-Tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 10,10-Dioxide 1:1 Maleate (**13**).

A mixture of **12** (1.00 g, 0.0026 mole), 10% palladium on activated charcoal (0.15 g), ethanol (80 ml) and glacial acetic acid (20 ml) was hydrogenated under 45 psi of pressure in a Parr apparatus at 45° for 48 hours. The catalyst was separated by filtration and the solvents were evaporated to a residue which was treated with crushed ice and 6*N* sodium hydroxide, then extracted with dichloromethane. The organic layer was separated, washed with brine and dried. Removal of the solvent gave a crude product which was purified on alumina column eluting with chloroform. The first fractions were discarded. The central eluates were collected and evaporated to give 0.61 g of **13** (80%) as an oil; ir (neat): ν 3320 cm^{-1} (NH); pmr: δ 1.81 (s, 1H, NH, disappeared on treatment with deuterium oxide), 2.96-3.60 (m, 6H, methylene groups), 4.63 (dd, 1H, J = 3 Hz, CH), 6.16 (m, 2H, pyrrole), 6.81-7.60 (m, 4H, pyrrole and benzene), 7.78-7.86 (m, 1H, benzene). A solution of compound **13** (0.48 g, 0.00165 mole) in 2 ml of absolute ethanol was added to a solution of maleic acid (0.19 g, 0.00165 mole) in the same solvent (2 ml). The mixture was stirred for 5 minutes, then filtered to yield 0.6 g of 1:1 maleate salt, mp 181-183° (after crystallization from absolute ethanol); ir (nujol): ν 1705 cm^{-1} (CO).

Anal. Calcd. for $C_{18}H_{19}N_3O_6S$: C, 53.32; H, 4.72; N, 10.36; S, 7.90. Found: C, 53.21; H, 4.64; N, 10.47; S, 8.01.

2-Methyl-1,3,4,14b-tetrahydro-2*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*]-[1,2,5]benzothiadiazepine 10,10-Dioxide (**7**).

A mixture of **13** (0.20 g, 0.0007 mole), 37% aqueous formaldehyde (0.1 ml), 10% palladium on activated charcoal (0.1 g) and ethanol (100 ml) was hydrogenated in a Parr apparatus under a pressure of 45 psi of hydrogen at room temperature for 4 hours. Removal of the catalyst by filtration and evaporation of the solvent gave a residue, which was dissolved in chloroform and dried. After filtration the organic solution was concentrated to a small volume and the crude product was purified on alumina column eluting with the same solvent. The first eluates were collected and evaporated to give 0.15 g of **7** (70%) as an oil which solidified on standing, mp 195-198° (after crystallization from toluene/ligroin); pmr: δ 2.25-2.98 [7H, overlapped signals, m, methylene groups, s (2.35), CH_3], 3.48 (m, 2H, methylene), 4.78 (dd, J = 4.5 Hz, CH), 6.18 (m, 2H, pyrrole), 6.81-7.61 (m, 4H, pyrrole and benzene), 7.75-7.90 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.64; N, 13.85; S, 10.56. Found: C, 59.54; H, 5.58; N, 13.66; S, 10.77.

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REFERENCES AND NOTES

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[1] S. Ankier, Progress in Medicinal Chemistry, Vol **23**, G. P. Ellis and G. B. West, eds, Elsevier, 1986, pp 121-185.

[2] M. Artico, S. Massa, A. Mai, R. Silvestri and G. Stefancich, *J. Heterocyclic Chem.*, **29**, 241 (1992).

[3] G. Stefancich, M. Artico and R. Silvestri, *J. Heterocyclic Chem.*, **29**, 487 (1992).

[4] G. Stefancich, M. Artico and R. Silvestri, *J. Heterocyclic Chem.*, **29**, 1005 (1992).

[5] M. Artico, R. Silvestri and G. Stefancich, *Synth. Commun.*, **22**, 1433 (1992).

[6] R. Silvestri, E. Pagnozzi, G. Stefancich and M. Artico, *Synth. Commun.*, in press.

[7] S. Massa, A. Mai and F. Corelli, *Tetrahedron Letters*, **29**, 6471 (1988).

[8] S. Massa, A. Mai, M. Artico, F. Corelli and M. Botta, *Tetrahedron*, **45**, 2763 (1989).

[9] S. Massa, M. Artico, A. Mai, F. Corelli, M. Botta, A. Tafi, G. C. Pantaleoni, R. Giorgi, M. F. Coppolino, A. Cagnotto and M. Skorupska, *J. Med. Chem.*, **35**, 4533 (1992).

[10] G. Stefancich and R. Silvestri, *J. Heterocyclic Chem.*, **26**, 745 (1989).

[11] G. Stefancich, M. Artico, R. Silvestri, G. C. Pantaleoni, R. Giorgi and G. Palumbo, *Farmaco*, **47**, 987 (1992).

[12] S. Massa, M. Artico, A. Mai, A. Mancuso and F. Corelli, *J. Heterocyclic Chem.*, **29**, 1851 (1992).

[13] F. Chimenti, S. Vomero, V. Nacci, M. Scalzo, R. Giuliano and M. Artico, *Farmaco, Ed. Sc.*, **29**, 589 (1974).

[14] A. Pictet and T. Spengler, *Chem. Ber.*, **44**, 2030 (1911).