Heterocycles with a Benzothiadiazepine Moiety. 3. Synthesis of Imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 9,9-Dioxide

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The synthesis of imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 9,9-dioxide (**5**), a novel sulfur-containing tetracyclic benzodiazepine, is reported starting from pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (**6**) by cycloaddition of tosylmethyl isocyanide to the azomethine double bond. Pyrrolobenzothiadiazepine **6** was obtained by iron powder/acetic acid reduction of 1-(2-nitrobenzenesulfonyl)pyrrole-2-carboxaldehyde (**7**) and subsequent ring closure of intermediate aminoaldehyde or by cyclization of 1-(2-formamidobenzenesulfonyl)pyrrole (**8**) with phosphorus oxychloride *via* a Bischler-Napieralski reaction. Formylation of 1-(2-aminobenzenesulfonyl)pyrrole with acetic-formic anhydride gave **8**. The structure of **5** was confirmed by oxidation with activated manganese dioxide of dihydro derivative **9**, obtained through cyclization of 11-aminomethyl-10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (**10**) with triethyl orthoformate. The last compound was prepared alternatively by catalytic reduction of nitro derivative **11**, obtained by addition of nitromethane to pyrrolobenzothiadiazepine **6**, or by lithium aluminum hydride/sulfuric acid reduction of amide **13**, synthesized starting from ethyl 10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-11-carboxylate 5,5-dioxide.

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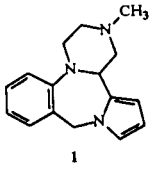
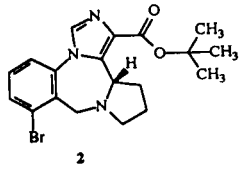
In recent years tetracyclic benzodiazepines have received great attention as psychotropic agents. Among these substances aptazepine **1** represents an antidepressant drug devoid of sedative activity [1] and bretazenil **2** is actually undergoing pharmacological screening as an anxiolytic agent [2].

As a chemical approach to new pyrrole-containing tetracyclic compounds we synthesized recently 10-methyl-10-azaaptazepine **3** [3] and tiaaptazepine 10,10-dioxide **4** [4], two novel tetracyclic compounds strictly related to aptazepine.



1



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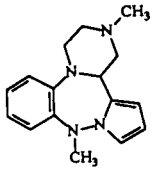

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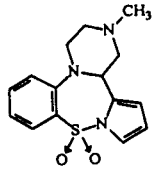

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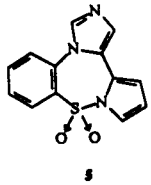
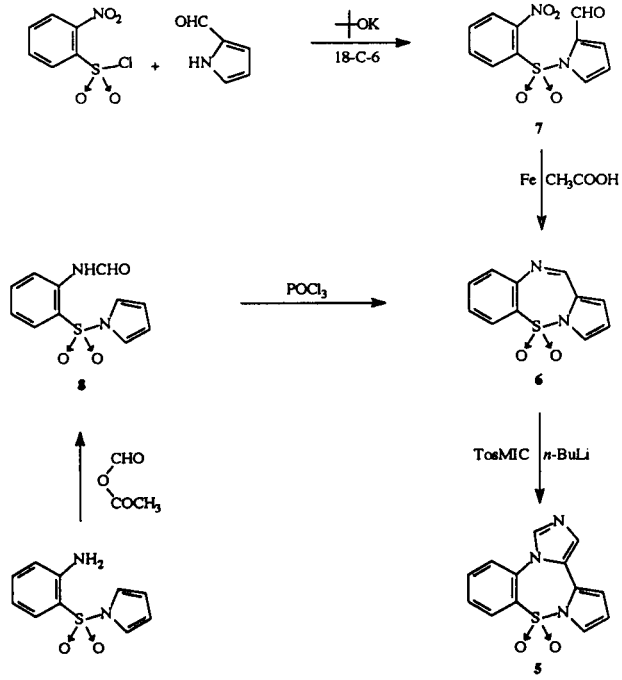


5

Pursuing our search on heterocycles with a benzothiadiazepine moiety [4,5] we report now the preparation of imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 9,9-dioxide (**5**), a novel tetracyclic ring of medicinal interest showing great structural affinities with the above compounds **1-4**.

Scheme 1

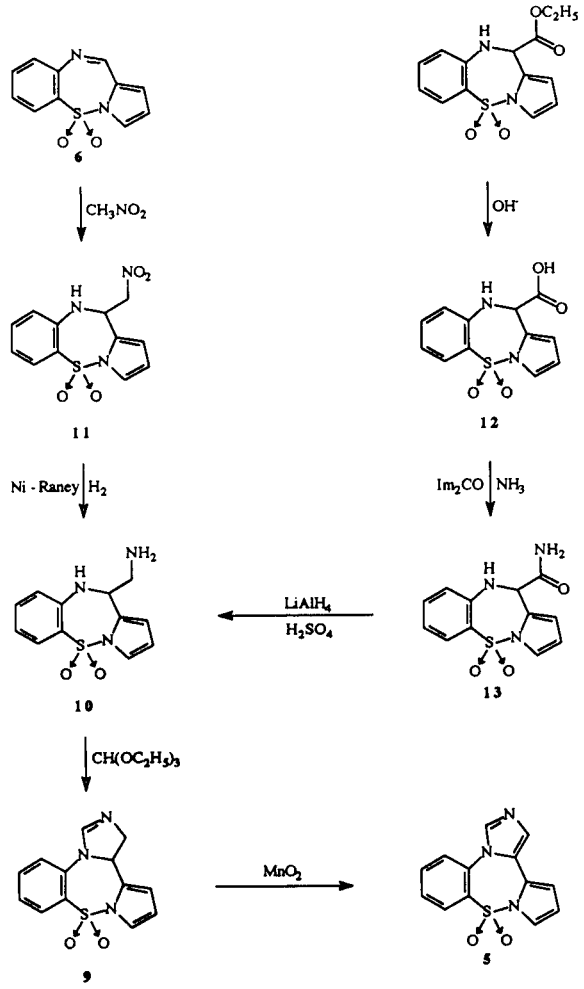


The synthesis of **5** was achieved by a simple procedure based on annelation at the 10,11 positions of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (**6**), by cycloaddition of tosylmethyl isocyanide (TosMIC) to the azomethine double bond in the presence of *n*-butyllithium in tetrahydrofuran at −72° [6] (Scheme 1).

The starting material **6** was obtained by iron powder-acetic acid reduction of 1-(2-nitrobenzenesulfonyl)pyrrole-2-carboxaldehyde (**7**) and concomitant ring closure of intermediate aminoaldehyde. In the present work the known nitroaldehyde **7** [7] was prepared starting from 2-nitrobenzenesulfonyl chloride and pyrrole-2-carboxaldehyde using potassium *tert*-butoxide and 18-crown-6 as a condensing agent.

Compound **6** was alternatively prepared starting from 1-(2-aminobenzenesulfonyl)pyrrole [7], which was reacted with acetic-formic anhydride to give 1-(2-formamidobenzenesulfonyl)pyrrole (**8**). Cyclization of **8** to **6** was achieved with phosphorous oxychloride *via* a Bischler-Napieralski reaction.

Scheme 2



Imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 9,9-dioxide (**5**) was also obtained by oxidation with manganese dioxide [8] of 1,13b-dihydroimidazo[5,1-*d*]pyrrolo-[1,2-*b*][1,2,5]benzothiadiazepine 9,9-dioxide (**9**), obtained by treating 11-aminomethyl-10,11-dihydropyrrolo[1,2-*b*]-[1,2,5]benzothiadiazepine 5,5-dioxide (**10**) with triethyl orthoformate (Scheme 2). The last compound was prepared by catalytic hydrogenation (Raney-Ni) of the corresponding nitroderivative **11**, which was obtained by addition of nitromethane to the azomethine double bond [9] of pyrrolobenzothiadiazepine **6**.

Alternatively, compound **10**, a useful intermediate for the synthesis of **5** *via* **9**, was prepared by a three-step procedure starting from ethyl 10,11-dihydropyrrolo[1,2-*b*]-[1,2,5]benzothiadiazepine-11-carboxylate 5,5-dioxide [4]. Alkaline hydrolysis of the last compound furnished the corresponding carboxylic acid **12**, which was condensed with dry gaseous ammonia in the presence of 1,1′-carbonyldiimidazole [10] to give the amide **13**, which in turn gave the required amine **10** by lithium aluminum hydride-sulfuric acid reduction.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. The nmr spectra were recorded with Varian EM-390 (90 MHz) and Gemini (200 MHz) spectrometers using tetramethylsilane as internal standard. Column chromatographies were performed on alumina Merck (70-230 mesh) 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 (approx. 20 bar). Elemental analyses were performed by laboratories of Professor A. Pietrogrande, University of Padova (Italy).

Imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 9,9-Dioxide (**5**).

From **6**.

n-Butyllithium (5.3 ml of 1.6 *M* solution in *n*-hexane, 0.0086 mole) was added dropwise into a solution of tosylmethyl isocyanide (0.84 g, 0.0043 mole) in dry tetrahydrofuran (10 ml) at −72° under nitrogen atmosphere. After 15 minutes a solution of **6** (1.00 g, 0.0043 mole) in dry tetrahydrofuran (10 ml) was added dropwise and stirring was continued at −72° for 30 minutes, then at room temperature for 60 hours. Water and ethyl acetate were added and the organic layer was separated, washed with brine and dried. Removal of the solvent gave a residue which was purified on silica gel column eluting with ethyl acetate. The central eluates were collected and evaporated to give **5** (0.45 g, 39%), mp

199-201° (after crystallization from aqueous ethanol); nmr spectra (Varian Gemini 200 MHz - deuteriochloroform): pmr δ 6.32-6.36 (m, 1H, β-pyrrole), 6.54-6.55 (m, 1H, β-pyrrole), 7.38-7.39 (m, 1H, α-pyrrole), 7.43 (s, 1H, imidazole), 7.54-7.61 (m, 2H, benzene), 7.75-7.83 (m, 1H, benzene), 7.99 (s, 1H, imidazole) 8.16-8.21 ppm (m, 1H, benzene); ^{13}C-nmr: δ 111.7, 113.0, 114.1, 120.85, 124.6, 125.5, 127.6, 128.0, 130.0, 132.5, 133.9, 135.7, 137.3 ppm.

Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49; S, 11.82. Found: C, 57.43; H, 3.29; N, 15.34; S, 11.90.

From **9**.

A mixture of **9** (0.16 g, 0.0006 mole), activated manganese dioxide (1.0 g, 0.011 mole) and acetone (40 ml) was refluxed overnight. After filtration the solvent was evaporated and the residue was purified on silica gel column eluting with ethyl acetate. Central eluates were collected and evaporated to give **5** (0.09 g, 56%), mp, ir and pmr spectral data were identical to those of the sample prepared from **6**.

Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-Dioxide (**6**).

From **7**.

Iron powder (30.6 g) was added over a period of 1 hour to a water-cooled solution of **7** (22.50 g, 0.080 mole) in glacial acetic acid (300 ml) and tetrahydrofuran (100 ml), then the mixture was stirred for 3.5 hours. Water and ethyl acetate were added and the organic layer was separated, washed with saturated sodium hydrogen carbonate solution, with brine and dried. Removal of the solvent gave a crude product which was purified on silica gel column eluting with ethyl acetate. Evaporation of the solvent from central eluates gave **6** (20.4 g, 92%), mp 109-110° (after crystallization from benzene/cyclohexane); pmr (deuteriochloroform): δ 6.46 (t, 1H, pyrrole), 6.90 (m, 1H, pyrrole), 7.33-7.83 (m, 4H, pyrrole and benzene), 8.13 (m, 1H, benzene), 8.66 ppm (s, 1H, N=CH-).

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.89; H, 3.47; N, 12.06; S, 13.80. Found: C, 57.10; H, 3.41; N, 11.93; S, 13.86.

From **8**.

A solution of **8** (11.60 g, 0.056 mole), phosphorus oxychloride (113 ml) and 1,2-dichlorethane (113 ml) was refluxed for 4.5 hours. Removal of the solvent gave a residue which was treated with crushed ice and 30% ammonium hydroxide solution. After extraction with ethyl acetate, the organic layer was separated, washed with brine and dried. Evaporation of the solvent gave a residue which was purified on alumina column eluting with chloroform. Central eluates were collected and evaporated to furnish **6** (5.0 g, 47%); after crystallization from benzene/cyclohexane, mp, ir and nmr spectral data were identical to those of the sample prepared from **7**.

1-(2-Nitrobenzenesulfonyl)pyrrole-2-carboxaldehyde (**7**).

A solution of pyrrole-2-carboxaldehyde (14.36 g, 0.150 mole) in dry tetrahydrofuran was added dropwise to a well-stirred mixture of potassium *tert*-butoxide (20.20 g, 0.180 mole) and 18-crown-6 (3.96 g, 0.018 mole) in the same solvent (300 ml). After 15 minutes, a solution of 2-nitrobenzenesulfonyl chloride (33.24 g, 0.150 mole) in dry tetrahydrofuran (300 ml) was added dropwise into the mixture cooled to 0°. After stirring at room temperature overnight, the solution was concentrated to a small volume. Extraction with dichloromethane followed by washing with brine, drying and evaporation of the solvent gave a crude product which was purified on alumina column eluting with chloroform. Evaporation of the solvent from central eluates gave 37.10 g of **7** (67%), mp 139-141° (after crystallization from benzene), lit [7], mp 137-138°, yield 50%.

1-(2-Formamidobenzenesulfonyl)pyrrole (**8**).

Formic acid (98-100%, 3.8 ml) was dropped onto acetic anhydride (8.5 ml) at 0° and the solution was stirred at room temperature for 2 hours. The solution was then added to a solution of 1-(2-aminobenzenesulfonyl)pyrrole [7] (10.00 g, 0.045 mole) in dry tetrahydrofuran (70 ml) and reaction was stirred at room temperature for 24 hours. After evaporation of the solvent, methanol (50 ml) was added and the mixture was stirred for 30 minutes. Removal of methanol gave a residue which was triturated with toluene and filtered to give 1-(2-formamidobenzenesulfonyl)-pyrrole (**8**) (11.4 g, 100%), which was crystallized from toluene/cyclohexane, mp 127°; ir (nujol): ν 1665 (CO), 3300 cm^{-1} (NH); pmr (deuteriochloroform): δ 6.30 (t, 2H, β-pyrrole), 7.10-7.96 (m, 5H, α-pyrrole (t) and benzene), 8.46-8.66 (m, 2H, benzene and CHO), 9.43 ppm (s, 1H, NH, disappeared on treatment with deuterium oxide).

Anal. Calcd. for $C_{11}H_{10}N_2O_3S$: C, 52.79; H, 4.03; N, 11.19; S, 12.81. Found: C, 52.85; H, 3.98; N, 10.90; S, 13.05.

1,13b-Dihydroimidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 9,9-Dioxide (**9**).

A solution of **10** (1.00 g, 0.0038 mole) in triethyl orthoformate (10 ml) was refluxed for 2 hours. Solvent was evaporated and the residue was purified on silica gel column eluting with ethyl acetate. Central eluates were collected and evaporated to furnish **9** (0.59, 57%), mp 190-192° (after crystallization from ethanol); pmr (deuteriochloroform): δ 4.33 (dd, 2H, J = 1.5 Hz, J = 9 Hz, CH_2), 6.11 (t, 1H, J = 9 Hz, CH), 6.25 (m, 2H, pyrrole), 6.98-7.65 (m, 5H), 8.08 ppm (m, 1H).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.12; H, 4.05; N, 15.37; S, 11.73. Found: C, 57.05; H, 4.08; N, 15.56; S, 11.47.

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

From **11**.

A mixture of **11** (0.20 g, 0.00068 mole) in tetrahydrofuran (40 ml) and methanol (20 ml) was hydrogenated for 24 hours at an initial pressure of 155 psi, using Raney-Nickel (0.6 ml of water suspension, Fluka catalogue 83440) as catalyst. The solid was removed by filtration on Celite® 545 (Fluka catalogue 22140) and the solution was concentrated to a small volume. Extraction with dichloromethane followed by washing with brine, drying and evaporation of the solvent gave a residue which was purified on alumina column eluting with ethyl acetate/ethanol 1:1. Central eluates were collected and evaporated to give **10** as thick oil (0.10 g, 56%); ir (neat): ν 3300, 3360 cm^{-1} (NH_2); pmr (deuteriochloroform): δ 1.60 (s, 2H, NH_2, disappeared on treatment with deuterium oxide), 3.55 and 3.58 (2q, AB part of ABX pattern, JAB = 12 Hz, CH_2), 5.23 (q, 1H, X part of ABX pattern, JAX = 9 Hz, JBX = 4.5 Hz, CH), 5.86-6.06 [m, 2H, pyrrole and NH (disappeared on treatment with deuterium oxide)], 6.20 (t, 1H, pyrrole), 6.56-6.76 (m, 2H, benzene), 7.13-7.40 (m, 2H, pyrrole and benzene), 7.80 ppm (m, 1H, benzene).

From **13**.

Concentrated sulphuric acid (0.58 ml) was carefully added dropwise over a period of 3 minutes onto an ice-cooled suspension of lithium aluminum hydride (0.89 g, 0.023 mole) in dry tetrahydrofuran (18 ml). After stirring at room temperature for 30 minutes, a solution of **13** (1.00 g, 0.0036 mole) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was kept at room temperature for 4 hours, then cooled to −15° while 2*N* sodium hydroxide solution (7.0 ml) was added dropwise. The solid which formed was separated by filtration, washed with tetrahydrofuran and discarded. The solution was concentrated to a small volume, extracted with chloroform, washed with brine and dried. Evaporation of the solvent gave a residue which was chromatographed on alumina column eluting with ethyl acetate/ethanol 9:1. The first eluates were discarded, then further elution with ethyl acetate/ethanol 1:1 furnished **10** after evaporation of the solvent (0.58 g, 61%); mp, ir and nmr spectral data were identical to those of the sample prepared from **11**.

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

A solution of **6** (1.00 g, 0.0043 mole) and nitromethane (9.6 ml) in ethanol (28.8 ml) was refluxed for 24 hours. After evaporation to dryness, the residue was purified on alumina column eluting with chloroform/ethanol 9:1. The central eluates were collected and evaporated to give **11** (0.6 g, 47%), mp 131-132° (after crystallization from benzene/cyclohexane); ir (nujol): ν 3330 cm^{-1} (NH).

Anal. Calcd. for $C_{12}H_{11}N_2O_4S$: C, 51.60; H, 3.97; N, 10.03; S, 11.48. Found: C, 51.38; H, 3.70; N, 10.12; S, 11.72.

10,11-Dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-11-carboxylic Acid 5,5-Dioxide (**12**).

A mixture of ethyl 10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-11-carboxylate 5,5-dioxide [4] (1.75 g, 0.0057 mole), 1*N* potassium hydroxide solution (7.1 ml), ethanol (20 ml) and tetrahydrofuran (20 ml) was stirred at room temperature for 3 hours, then poured onto crushed ice. After acidification with 1*N* hydrochloric acid until *p*H 2 and extraction with ethyl acetate, the organic layer was washed with brine, dried and evaporated. The oily residue was triturated with toluene and the solvent was evaporated to give **12** (1.33 g, 84%), mp 159-162° (after crystallization from toluene); ir (nujol): ν 1720 (CO), 3330 cm^{-1} (NH); pmr (hexadeuteriodimethyl sulfoxide): δ 5.80 (d, 1H, J = 3 Hz, CH), 6.20-6.43 (m, 2H, pyrrole), 6.63-6.86 (m, 1H, benzene), 7.06-7.53 [m, 4H, pyrrole, benzene and NH (disappeared on treatment with deuterium oxide)], 7.60-7.76 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.06; S, 11.62. Found: C, 52.05; H, 3.50; N, 10.13; S, 11.55.

10,11-Dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-11-carboxyamide 5,5-Dioxide (**13**).

1,1'-Carbonyldiimidazole (0.87 g, 0.0054 mole) was added portionwise to a water-cooled solution of **12** (1.00 g, 0.0036 mole) in dry tetrahydrofuran (50 ml) and the mixture was stirred at room temperature for 2 hours. Dry gaseous ammonia was bubbled through for 1 hour while stirring at room temperature. After concentration to a small volume, the mixture was extracted with ethyl acetate, washed with brine and dried. Evaporation of the solvent gave a crude product which was purified by crystallization from toluene to give **13** (0.50 g, 50%), mp 214-216°; ir (nujol): ν 1690 (CO), 3300, 3400 cm^{-1} (NH_2); pmr (hexadeuteriodimethyl sulfoxide): δ 5.86 (d, 1H, J = 3 Hz, CH), 6.20 (m, 1H, pyrrole), 6.40 (t, 1H, pyrrole), 6.70-7.03 [m, 2H, benzene and NH (disappeared on treatment with deuterium oxide)], 7.20-7.63 (m, 3H, pyrrole and benzene), 7.70-7.93 [m, 2H, benzene and $CONH_2$ (disappeared on treatment with deuterium oxide)], 8.26 ppm (s, 1H, $CONH_2$, disappeared on treatment with deuterium oxide).

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 4.00; N, 15.15; S, 11.56. Found: C, 52.10; H, 3.95; N, 15.02; S, 11.68.

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