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Heterocycles with a Benzothiadiazeypine Moiety. I. Synthesis of Pyrrolo[1,2-b]-s-triazolo[3,4-d][1,2,5]benzothiadiazepine 5,5-Dioxide

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HETEROCYCLES WITH A BENZOTHIADIAZEYPINE MOIETY 1. SYNTHESIS OF PYRROLO[1,2-b]-*s*-TRIAZOLO[3,4-d] [1,2,5]BENZOTHIADIAZEPINE 5,5-DIOXIDE

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Abstract: Condensation of 2-nitrobenzenesulfonyl chloride with 2-ethoxycarbonyl--1H-pyrrole in the presence of potassium *tert*-butoxide and 18-crown-6 furnished 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)-1H-pyrrole. Reduction of nitro group to amino and subsequent cyclization by heating the aminoester in the presence of 2-hydroxypyridine as a bifuctional catalyst led to 11-oxo(10H)-pyrrolo[1,2-b] [1,2,5]benzothiadiazepine 5,5-dioxide. Treatment of the latter compound with di-4-morpholinylphosphinic chloride gave the corresponding phosphinyloxyimine, which on reacting with formylhydrazine underwent intramolecular cyclization to afford the title tetracyclic ring.

Tetracyclic benzodiazepines have been widely investigated in the last decade and some of them received great attention as psychotropic drugs. Mianserine **1** and aptazepine **2** have been found to be strongly efficacious as antidepressant agents[1] and bretazenil **3** is actually ongoing clinical trials as anxiolytic drug[2,3].

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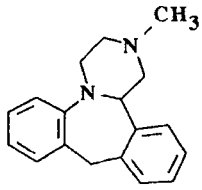
As far as regards our knowledge no search has been devoted to the synthesis of pyrrolobenzothiadiazepines annelated with azole rings. We therefore decided to start a study in this direction as a further development of our recent search in the chemistry field of tetra-annelated heterocycles [4-9].



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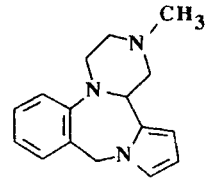

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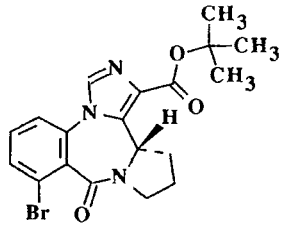

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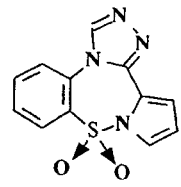

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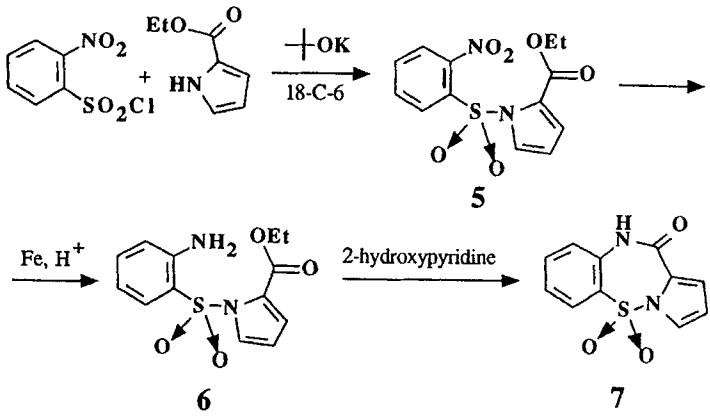
Following a procedure proposed by one of us some years ago[10], we have realized in the present work the synthesis of pyrrolo[1,2-b]-*s*-triazolo[3,4-d][1,2,5]benzothiadiazepine **4** , a novel tetracyclic ring with pyrrolobenzothiadiazepine moiety annelated with 1,2,4-triazole.

Condensation of 2-nitrobenzenesulfonyl chloride with 2-ethoxycarbonyl-1H-pyrrol11 in the presence of potassium *tert*-butoxide and 18-crown-6 furnished 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)-1H-pyrrole **5** , which was reduced with iron powder in glacial acetic acid to the corresponding aminoderivative **6**. The latter compound was then cyclized to the lactam **7** by heating in the presence of 2-hydroxypyridine as a bifunctional catalyst (Scheme 1).

Treatment of 11-oxo(10H)pyrrolo[2,1-c][1,2,5]benzothiadiazepine 5,5-dioxide **7** with di-4-morpholinylphosphinic chloride[12] in the presence of sodium hydride afforded the phosphinyloxyimine **8** ,

SCHEME 1



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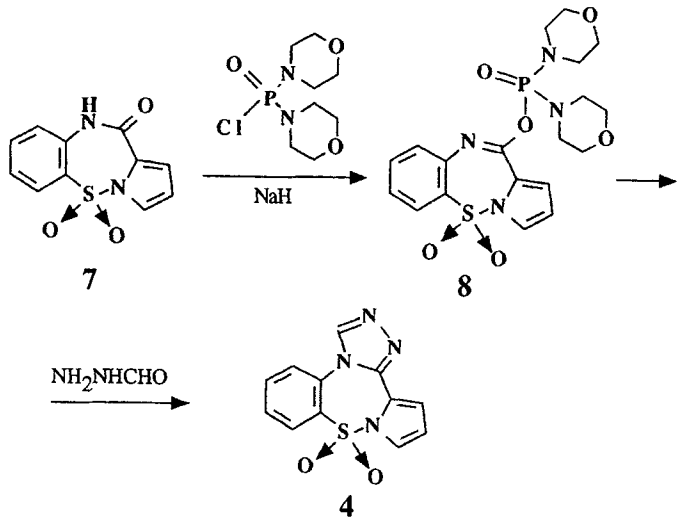

which was transformed into the title tetracyclic derivative **4** by reacting with formylhydrazine at reflux in *n*-butanol (Scheme 2).

The last reaction involved displacement of the di-4-morpholinylphosphinyloxy group by formylhydrazine with

concomitant intramolecular ring closure of formylhydrazino intermediate.

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal IA6304 apparatus and are uncorrected. Infrared spectra were run a on a Perkin-Elmer 1310 spectrophotometer in nujol mulls. The pmr spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as internal standard. Column chromatography purifications were performed on silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh). Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminum oxide precoated plates with fluorescent indicator) 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 (Buchi) operating at reduced pressure (approx. 20 bar). Elemental analyses were performed by Laboratories of Prof. A. Pietrogrande, University of Padova (Italy).

2-Ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)-1H-pyrrole (5). A solution of 2-ethoxycarbonyl-1H-pyrrole (20.85 g, 0.15 mol) in dry tetrahydrofuran (320 ml) was added dropwise to a well-stirred mixture of 18-crown-6 (4.23 g, 0.016 mol) and potassium *tert*-butoxide (20.20 g, 0.15 mol) in the same solvent (320 ml). After 15 minutes a solution of 2-nitrobenzenesulfonyl chloride (33.24 g,0.15 mol) in dry tetrahydrofuran (320 ml) was slowly dropped onto the ice-cooled suspension. Stirring was continued at room temperature for 2.5 hours. After concentration, water and dichloromethane were added with shaking. The organic layer was separated, washed with brine and dried. Removal of the solvent gave a residue which was purified on alumina column eluting with chloroform. First fractions were discarded and central eluates were collected and evaporated to give **5** (31.62 g, 65%), mp 120-122°C after recrystallization from benzene/cyclohexane; ir: 1710 cm^{-1} (C=O); pmr ($CDCl_3$): δ 1.20 (t, 3H, $COOCH_2C\underline{H}_3$), 4.15 (q, 4H, $COOC\underline{H}_2CH_3$), 6.35 (m, 1H, pyrrole), 7.15 (m, 1H, pyrrole), 7.65-7.91 (m, 4H, pyrrole and benzene), 8.25-8.41 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{13}H_{12}N_2O_6S$: C, 48.14; H, 3.73; N, 8.63; S, 9.88. Found: C, 47.87; H, 3.68; N, 8.35; S, 9.62.

2-Ethoxycarbonyl-1-(2-aminobenzenesulfonyl)-1H-pyrrole (6). Iron powder (15 g) was added over a period of 1 hour to a solution of nitroester **5** (16.21 g, 0.05 mol) in glacial acetic acid (200 ml) under stirring while heating at 60°C. Stirring was continued at 60°C for 2 hours. After removal of the solvent the residue was extracted with ethyl acetate. The organic extracts were washed with brine and dried. Evaporation of the solvent furnished pure **6** (11.77 g, 80%), mp 95-97°C after recrystallization from aqueous ethanol; ir: 3470, 3360 cm^{-1} (NH_2) and 1710 (C=O); pmr ($CDCl_3$): δ 1.20 (t, 3H, $COOCH_2C\underline{H}_3$), 4.20 (q, 4H, $COOC\underline{H}_2CH_3$), 5.16 (s broad, 2H, NH_2; disappeared on treatment with deuterium oxide), 6.26 (m, 1H, pyrrole), 6.61-6.83 (m, 2H, benzene), 7.06 (m, 1H, pyrrole), 7.20-7.43 (m, 1H, benzene), 7.60-7.76 ppm (m, 2H , pyrrole and benzene).

Anal. Calcd. for $C_{13}H_{14}N_2O_4S$: C, 53.04; H, 4.79; N, 9.51; S, 10.89. Found: C, 53.24; H, 4.86; N, 9.29; S,11.00.

11-Oxo(10H)-pyrrolo[2,1-c][1,2,5]benzothiadiazepine 5,5-dioxide (7). A well-stirred mixture of **6** (10.0 g, 0.034 mol) and 2-hydroxypyridine (3.23 g, 0.034 mol) was heated at 170°C while stirring for 48 hours under nitrogen stream. After cooling, the crude residue was dissolved in chloroform and purified on alumina column eluting with the same solvent. First eluates were discarded and elution was continued with chloroform/ethanol (9:1). Second eluates after evaporation of the solvent gave **7** (5.06 g, 60%), mp 292-293°C after recrystallization from ethanol; ir: 1640 cm^{-1} (C=O); pmr (DMSO-d_6): δ 6.51 (m, 1H, pyrrole), 7.16 (m, 1H, pyrrole) 7.35-8.15 (m, 5H, pyrrole and benzene), 11.15 ppm (s broad, 1H, NH-CO).

Anal. Calcd. for $C_{11}H_8N_2O_3S$: C, 53.21; H, 3.24; N, 11.28; S, 12.91. Found: C, 53.32; H, 3.25; N, 11.15; S, 12.77.

11-(Di-4-morpholinylphosphinyloxy)pyrrolo[2,1-c][1,2,5]benzothiadiazepine 5,5-dioxide (8). A 80% dispersion of sodium hydride in white oil (0.63 g, 0.021 mol) was added to a stirred solution of lactam **7** (2.60 g, 0.0105 mol) in dry tetrahydrofuran (150 ml) and the mixture was stirred at room temperature for 2 hours. Di-4-morpholinylphosphinic chloride (5.33 g, 0.021 mol) was then added at 0°C and stirring was continued at room temperature for 4 hours.Insoluble salts were removed by filtration and solvent was evaporated to give a residue, which was purified by chromatography on silica gel column eluting with ethyl

acetate/ethanol (9:1). First fractions were discarded, then central eluates were collected and evaporated to yield **8** (1.95 g, 40%), mp 234-237°C after recrystallization from 2-propanol/ethyl acetate (+4°C); ir: 1255 cm^{-1} (P=O); pmr ($CDCl_3$): δ 3.20-3.46 (m, 8H, morpholine), 3.63-3.85 (m,8H, morpholine), 6.45 (m, 1H, pyrrole), 6.61 (m, 1H, pyrrole), 7.30-7.83 (m, 4H, pyrrole and benzene), 8.00-8.16 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{19}H_{23}N_4O_6PS$: C, 48.92; H, 4.97; N, 12.01; P, 6.64; S, 6.87. Found: C, 49.02; H, 4.99; N, 11.85; P, 6.78; S, 6.68.

Pyrrolo[1,2-b]-*s*-[3,4-d][1,2,5]benzothiadiazepine 5,5-dioxide (4). A solution of phosphinyloxyimine **8** (1.07 g, 0.0023 mol) and formylhydrazine (0.27 g, 0.0046 mol) in *n*-butanol (21 ml) was heated at reflux for 16 hours. The solvent was evaporated and the residue partitioned between dichloromethane and brine. The organic layer was separated and dried. Removal of the solvent gave a residue which was triturated with ethanol and filtered to give pure **4** (0.53 g, 85%), mp 272-275°C after recrystallization from ethanol; pmr (DMSO-d_6): δ 6.61 (m, 1H, pyrrole), 7.15 (m, 1H pyrrole), 7.68-7.98 (m, 2H, pyrrole and benzene), 8.12 (m, 2H, benzene), 8.25-8.40 (m, 1H, benzene), 9.48 ppm (s, 1H, triazole).

Anal. Calcd. for $C_{12}H_8N_4O_2S$: C, 52.93; H, 2.96; N, 20.57; S, 11.77. Found: C, 53.10; H, 3.07; N, 20.34; S, 11.64.

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