Synthesis of 9*H*-Pyrrolo[2,1-*b*][1,3,6]benzothiadiazocin-10(11*H*)-one 4,4-Dioxide, a Potential anti-HIV-1 Agent

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Starting from 2-(2-aminophenylthio)-1-ethoxycarbonylmethyl-1*H*-pyrrole a four-step synthesis of 9*H*-pyrrolo[2,1-*b*][1,3,6]benzothiadiazocin-10(11*H*)-one 4,4-dioxide, a new heterocycle related to anti-HIV-1 tricyclic non-nucleoside agents, is described.

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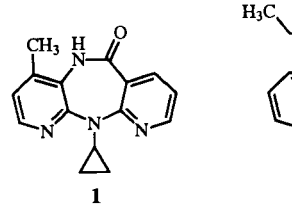
Searches for new non-nucleoside agents capable to inhibit the reverse transcriptase (RT) enzyme, which is required for the multiplication of HIV-1 retrovirus, are widely developed today with the aim to contribute to the resolution of the problems associated with the therapy of AIDS [1].

After the discovery of nevirapine **1** [2] various derivatives of tricyclic systems which incorporate a diazepine moiety were studied and tested as anti-HIV-1 agents [3], whereas the related systems containing a diazocine ring have not yet been explored as inhibitors of retroviruses responsible for AIDS.

Following our searches on tricyclic systems having a pyrrole moiety we decided to prepare 9*H*-pyrrolo[2,1-*b*][1,3,6]benzothiadiazocin-10(11*H*)-one 4,4-dioxide **5**, a new heterocyclic system mimicking the main chemical features of some newly reported anti HIV-1 agents, such as compounds **1**, **2** [4], **3** [5] and **4** [6].

The synthesis of **5** has been carried out as follows. 2-Aminothiophenol was reacted with the ethyl ester of 1*H*-pyrrole-1-acetic acid [7] in the presence of iodine and potassium iodide as reported by Beveridge and Harris [8] to afford a mixture of 2-(2-aminophenylthio)-1-ethoxycarbonylmethyl-1*H*-pyrrole (**6**) and 3-(2-aminophenylthio)-1-ethoxycarbonylmethyl-1*H*-pyrrole (**7**).

Alkaline hydrolysis of **6** gave the related acid **8** which was cyclized intramolecularly by treatment with *N*-(3-



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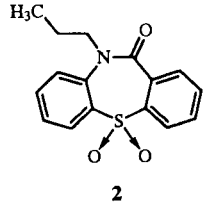

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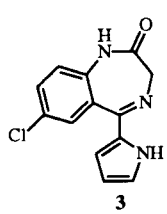

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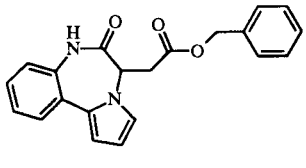

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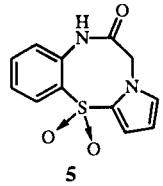

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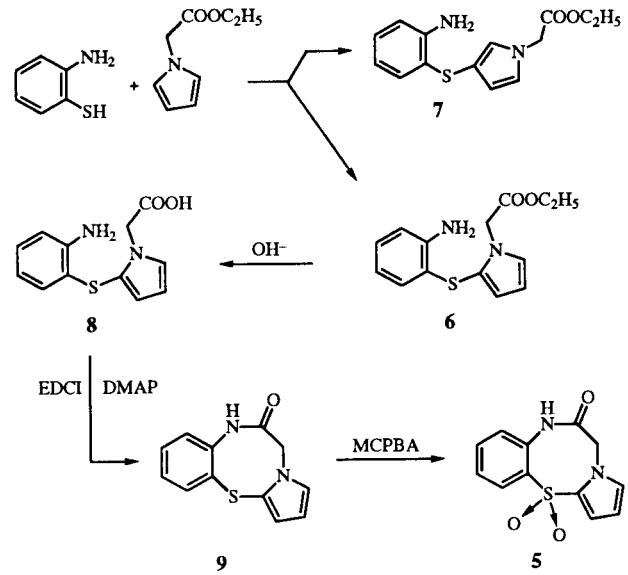
Scheme 1



dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) to yield the tricyclic pyrrolobenzothiadiazocine **9**. Oxidation of sulfur to sulfone was accomplished by treating **9** with 3-chloroperoxybenzoic acid (MCPBA) with formation of the title compound **5** (Scheme 1).

In vitro assays to evaluate anti-HIV-1 activity of **5** are carried out by Professor P. La Colla at University of Cagliari.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra (nujol mulls) were run on a Perkin-Elmer 1310 spectrophotometer. The ^{1}H-nmr spectra were recorded with Varian EM-390 (90 MHz) and with Varian Gemini (200 MHz) spectrometers using tetramethylsilane as the internal standard. Column chromatography was carried out on alumina 90 Merck and silica gel 60 Merck (particle size 63-200 μm). The mplc was performed on silica gel 60 Merck (particle size 15-40 μm) by using a Büchi 681 chromatography pump. 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.

2-(2-Aminophenylthio)-1-ethoxycarbonylmethyl-1*H*-pyrrole (**6**) and 3-(2-Aminophenylthio)-1-ethoxycarbonylmethyl-1*H*-pyrrole (**7**).

A solution of iodine (25.38 g, 0.10 mole) and potassium iodide (79.68 g, 0.48 mole) in water (100 ml) was added dropwise to a well-stirred solution of 2-aminothiophenol (12.52 g, 0.10 mole) and 1-ethoxycarbonylmethyl-1*H*-pyrrole [7] (15.31 g, 0.10 mole) in *N,N*-dimethylformamide (150 ml) and water (150 ml). The reaction was maintained at room temperature for 1 hour, then diluted with water (900 ml) and neutralized by adding solid sodium hydrogen carbonate. After extraction with ethyl acetate, the organic layer was washed with brine and dried. Removal of the solvent left a residue which was purified by mplc (silica gel, dichloromethane/petroleum ether 1:1). Evaporation of the solvent from the first fractions furnished **6** (19.6 g, 71%) as an oil which solidified on standing, mp 58-60° (after crystallization from ligroin); ir: ν 1740 (CO), 3340, 3440 cm^{-1} (NH_2); ^{1}H-nmr (90 MHz) (deuteriochloroform): δ 1.13 (t, 3H, $COOCH_2CH_3$), 4.00 (q and broad, overlapped signals, 4H, $COOCH_2CH_3$ and NH_2, disappeared on treatment with deuterium oxide), 4.66 (s, 2H, CH_2), 6.23 (t, 1H, pyrrole), 6.50-7.30 ppm (m, 6H, pyrrole and benzene). Further elution with the same solvent afforded **7** (6.0 g, 22%) as a thick oil; ir: ν 1730 (CO), 3340, 3440 cm^{-1} (NH_2); ^{1}H-nmr (90 MHz) (deuteriochloroform): δ 1.03 (t, 3H, $COOCH_2CH_3$), 3.86 (q, 2H, $COOCH_2CH_3$), 4.13 (broad, 2H, NH_2, disappeared on treatment with deuterium oxide), 4.58 (s, 2H, CH_2), 6.53-6.73 (m, 4H, aromatic), 6.90-7.30 ppm (m, 3H, aromatic).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$ (276.35): C, 61.06; H, 5.83; N, 10.13; S, 11.60. Found for **6**: C, 60.86; H, 5.54; N, 10.09; S, 11.87. Found for **7**: C, 61.22; H, 5.91; N, 9.98; S, 11.41.

2-(2-Aminophenylthio)-1*H*-pyrrole-1-acetic Acid (**8**).

A solution of **6** (15.75 g, 0.057 mole), 1*N* potassium hydroxide (86 ml), ethanol (190 ml) and tetrahydrofuran (190 ml) was stirred at room temperature for 3.5 hours. After pouring on crushed ice, the mixture was made acid with 1*N* hydrochloric acid until *p*H 2 was reached and then shaken with ethyl acetate. Organic extracts were washed with brine and dried. Removal of the solvent furnished **8** (14.1 g, 95%) which was crystallized from toluene, mp 87-90°; ir: ν 1700 (CO), 3340, 3420 cm^{-1} (NH_2); ^{1}H-nmr (200 MHz) (hexadeuteriodimethyl sulfoxide): δ 4.69 (s (CH_2) and broad, disappeared on treatment with deuterium oxide, overlapped signals), 6.11 (t, 1H), 6.47 (m, 2H), 6.73 (m, 1H), 6.90-7.01 (m, 3H), 7.42 (m broad) 7.97 ppm (m broad).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$ (248.30): C, 58.04; H, 4.87; N, 11.28; S, 12.91. Found: C, 57.87; H, 4.90; N, 11.21; S, 13.03.

9*H*-Pyrrolo[2,1-*b*][1,3,6]benzothiadiazocin-10(11*H*)-one (**9**).

A mixture of **8** (10.00 g, 0.040 mole), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) (7.66 g, 0.040 mole), 4-dimethylaminopyridine (DMAP) (4.88 g, 0.040 mole) and dichloromethane (400 ml) was stirred at room temperature for 64 hours, then diluted with water. After shaking the organic layer was separated, washed with 1*N* hydrochloric acid, then with brine and dried. Removal of the solvent furnished the crude residue which was purified on silica gel column (ethyl acetate as eluent) affording **9** (5.0 g, 54%), mp 239-243° (after crystallization from toluene); ir: ν 1670 cm^{-1} (CO); ^{1}H-nmr (90 MHz) (hexadeuteriodimethyl sulfoxide): δ 4.18 (s, 2H, CH_2), 6.05 (t, 1H, pyrrole), 6.26 (q, 1H, pyrrole), 6.95 (t, 1H, pyrrole), 7.28-7.91 (m, 4H, benzene), 12.08 ppm (s, 1H, NH, disappeared on treatment with deuterium oxide).

Anal. Calcd. for $C_{12}H_{10}N_2OS$ (230.28): C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.55; H, 4.26; N, 12.03; S, 13.82.

9*H*-Pyrrolo[2,1-*b*][1,3,6]benzothiadiazocin-10(11*H*)-one 4,4-Dioxide (**5**).

3-Chloroperoxybenzoic acid (MCPBA) (11.53 g of a 55% preparation, 0.036 mole) was added portionwise to a water-cooled solution of **9** (3.35 g, 0.014 mole) in chloroform (500 ml), then the mixture was stirred at room temperature overnight. After dilution with water, the organic layer was separated, washed with saturated sodium hydrogen carbonate solution, then with brine and dried. Removal of the solvent gave a residue which was purified by passing through a silica gel column (ethyl acetate/ethanol 9:1 as eluent). Evaporation of the solvent from the appropriate eluates furnished **5** (1.4 g, 38%), mp 268-271° (after crystallization from ethanol); ir: ν 1700 cm^{-1} (CO); ^{1}H-nmr (200 MHz) (hexadeuteriodimethyl sulfoxide): δ 4.38 (s, 2H, CH_2), 6.27 (m, 1H, pyrrole), 7.03 (m, 1H, pyrrole), 7.36-7.45 (m, 2H, pyrrole and benzene), 7.63 (t, 1H, benzene), 7.85 (t, 1H, benzene), 8.96 (d, 1H, benzene), 10.73 ppm (s, 1H, NH, disappeared on treatment with deuterium oxide).

Anal. Calcd. for $C_{12}H_{10}N_2O_3S$ (262.28): C, 54.94; H, 3.84; N, 10.68; S, 12.22. Found: C, 54.74; H, 3.80; N, 10.79; S, 12.39.

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