

Roberto Di Santo, Roberta Costi and Marco Artico

Dipartimento di Studi Farmaceutici, Facoltà di Farmacia, Università degli Studi di Roma "La Sapienza",
P.le A. Moro 5, I-00185 Roma, Italy

Silvio Massa

Dipartimento Farmaco Chimico Tecnologico, Università di Siena,
Banchi di Sotto 55, I-53100 Siena, Italy

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The synthesis of 10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocine 5,5-dioxide has been carried out by intramolecular cyclization of 1-(2-formamidomethylphenylsulfonyl)-1*H*-pyrrole, prepared from the reaction of 1-(2-aminomethylphenylsulfonyl)-1*H*-pyrrole with ethyl formate. Treatment of the last pyrrole derivative with triphosgene afforded 10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocin-12(11*H*)-one 5,5-dioxide, which was also prepared by cyclization of 1-(2-methoxycarbamidomethylphenylsulfonyl)-1*H*-pyrrole. Methylation of the 12-one derivative furnished the corresponding *N*₁₁-methyl benzothiadiazepine dioxide. 1-(2-Aminomethylphenylsulfonyl)-1*H*-pyrrole has been prepared by cleavage of the phthalimido moiety of 1-(2-phthalimidomethylphenylsulfonyl)-1*H*-pyrrole, obtained by reacting with potassium phthalimide 1-(2-bromomethylphenylsulfonyl)-1*H*-pyrrole. This compound has been obtained starting from 2-bromomethylbenzensulfonamide by Clauson-Kaas procedure.

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Tricyclic systems containing one or more heteroatoms have been largely investigated after the discovery of nevirapine **1** [1,2] a dipyrrolo-benzodiazepine derivative belonging to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

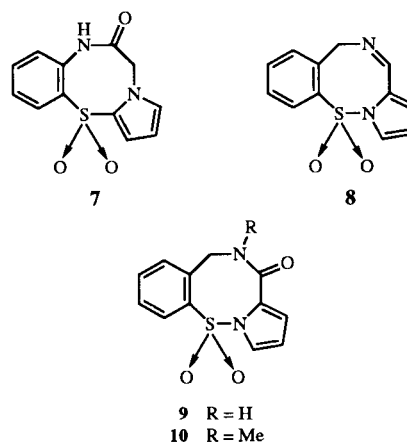
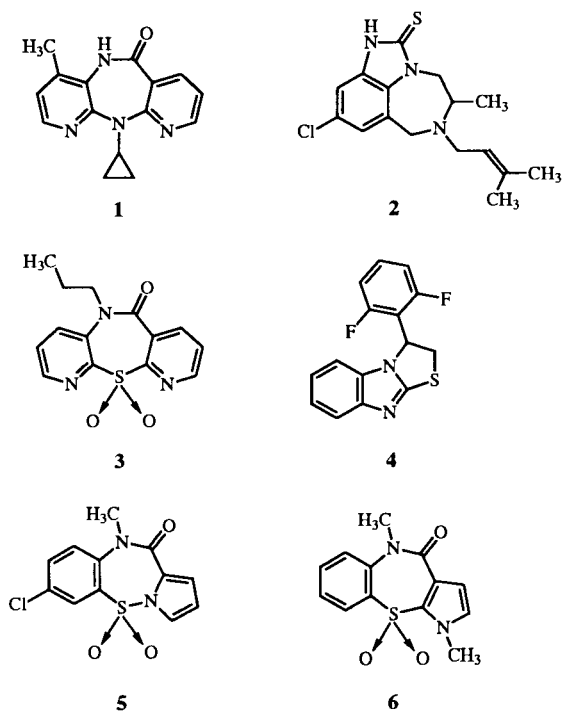
Development of 6,7,6- and 5,7,6-membered tricyclic systems led to the discovery of new potent anti-HIV-1 agents targeted at the reverse transcriptase (RT), such as compounds **2-6** [3-8] but poor attention was devoted to

6,8,5-membered tricyclic systems miming the chemical structure of compounds **1-6**.

To obviate to this omission, we recently described the synthesis of 9*H*-pyrrolo [2,1-*b*][1,3,6]benzothiadiazocin-10(11*H*)-one 4,4-dioxide **7** [9] a prototype model for design new potential anti-HIV-1 agents related to nevirapine **1** and its congeners **2-6**.

As a further development of our research, we report now the synthesis of 10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocine 5,5-dioxide **8**, a derivative of a novel heterocyclic system of pyrrolo-benzothiadiazocine series.

The synthesis of 10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocin-12(11*H*)-one 5,5-dioxide **9** and its *N*₁₁-methyl derivative **10** is also described.



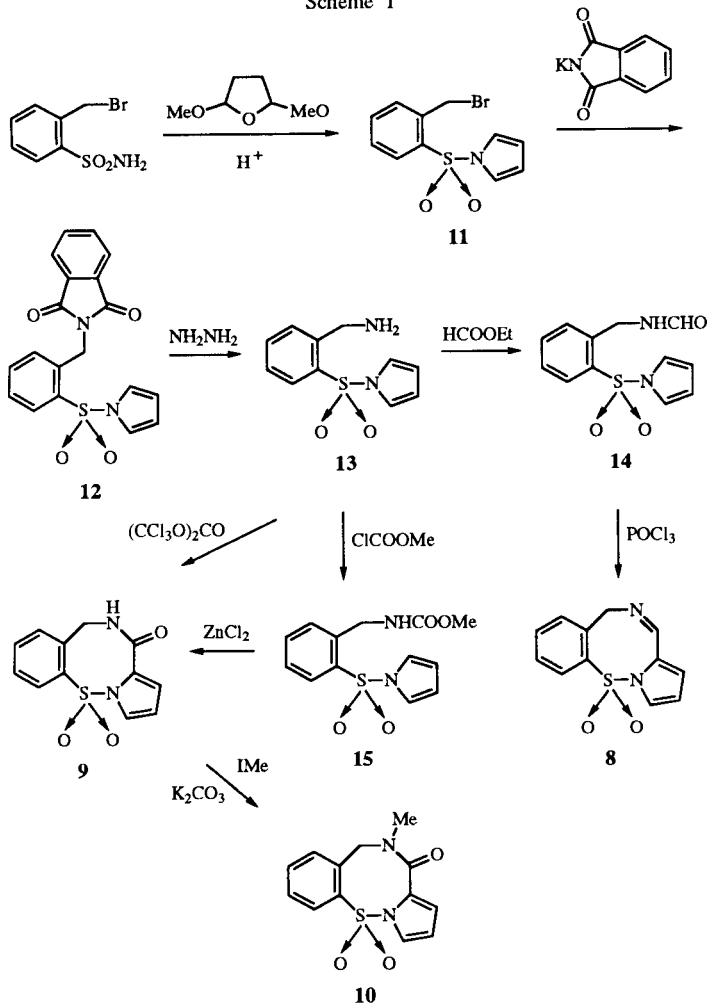
1-(2-Bromomethylphenylsulfonyl)-1*H*-pyrrole **11** was prepared by reacting 2-bromomethylbenzensulfonamide

with 2,5-dimethoxy tetrahydrofuran in glacial acetic acid. Treatment of **11** with potassium phthalimide in anhydrous dioxane in the presence of 18-crown-6 afforded 1-(2-phthalimidomethylphenylsulfonyl)-1*H*-pyrrole **12**, which was deprived of protecting phthalimido group to give the corresponding amino derivative **13** by reaction with hydrazine hydrate.

On reacting with ethyl formate and methyl chlorocarbonate amine **13** furnished derivatives **14** and **15**, respectively. Intramolecular cyclization of formamido derivative **14** by treating with phosphorus oxychloride at room temperature gave the title 10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocine 5,5-dioxide **8**.

A similar reaction using zinc chloride as the condensing agent led to 10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocin-12(11*H*)-one 5,5-dioxide **9** when the carbamoyl derivative **15** was employed as substrate. Derivative **9** was also obtained directly from the amine **13** by the action of bis(trichloromethyl)carbonate (triphosgene) (Scheme 1).

Scheme 1



EXPERIMENTAL

Melting points were determined on an Electrothermal IA6304 apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer 1310 spectrophotometer. The ¹H-nmr spectra were recorded with a Bruker AC200 (200 MHz) using tetramethylsilane as internal standard. Column chromatography purifications were performed on alumina Merck (70-230 mesh). Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator) was employed for tlc. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvents after reactions and extractions involved the use of a rotatory evaporator (Büchi) operating at reduced pressure (approximately 20 bar). Elemental analyses were performed by Laboratories of Professor A. Pietrogrande, University of Padova, Italy.

1-(2-Bromomethylphenylsulfonyl)-1*H*-pyrrole (**11**).

2-Bromomethylbenzenesulfonamide (0.2 g, 0.0008 mole) and 2,5-dimethoxytetrahydrofuran (0.18 ml, 0.0012 mole) were dissolved in glacial acetic acid (6 ml). The mixture was refluxed for 1 hour, then evaporated and the residue treated with water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic extracts were collected, washed with brine (3 x 50 ml) and dried. Removal of the solvent gave **11** (0.21 g, 88%), mp 72-73° (cyclohexane); ¹H-nmr (deuteriochloroform): δ 4.92 (s, 2H, CH₂), 6.35 (m, 2H, pyrrole β-H), 7.23 (m, 2H, pyrrole α-H) and 7.38-7.75 (m, 4H, benzene).

Anal. Calcd. for C₁₁H₁₀BrNO₂S: C, 44.02; H, 3.36; N, 4.67; S, 10.68; Br, 26.62. Found: C, 43.96; H, 3.38; N, 4.70; S, 10.68; Br, 26.67.

1-(2-Phthalimidomethylphenylsulfonyl)-1*H*-pyrrole (**12**).

Potassium phthalimide (0.73 g, 0.0034 mole) was added onto a well-stirred solution of **11** (1.0 g, 0.0033 mole) and 18-crown-6 (1.12 g, 0.0033 mole) in anhydrous dioxane (20 ml). The mixture was refluxed for 36 hours. After cooling the precipitate was removed by filtration and the solvent was evaporated to give **12** (0.58 g, 48%), mp 158-160° (absolute ethanol); ir: ν 1760, 1710 cm⁻¹ (C=O); ¹H-nmr (hexadeuteriodimethylsulfoxide): δ 5.15 (s, 2H, CH₂), 6.47 (m, 2H, pyrrole β-H), 7.35-8.05 (m, 10H, pyrrole α-H and benzene).

Anal. Calcd. for C₁₉H₁₄N₂O₄S: C, 62.29; H, 3.85; N, 7.65; S, 8.75. Found: C, 62.35; H, 3.90; N, 7.55; S, 8.68.

1-(2-Aminomethylphenylsulfonyl)-1*H*-pyrrole (**13**).

Hydrazine hydrate (0.06 g, 0.0012 mole) was added onto a well stirred suspension of **12** (0.23 g, 0.00063 mole) in boiling 95% ethanol (10 ml). The mixture was refluxed under stirring for 1 hour. After cooling the precipitate was removed by filtration and the solution was evaporated. The residue was purified by chromatography on alumina column (ethyl acetate-ethanol 1:1 as eluent) to afford **13** (0.075 g, 50%) as a yellow-brown oil; ir: ν 3340, 3100 cm⁻¹ (NH₂); ¹H-nmr (deuteriochloroform): δ 2.60 (bs, 2H, NH₂), 4.10 (s, 2H, CH₂), 6.24 (m, 2H, pyrrole β-H), 7.03-7.65 (m, 6H, pyrrole α-H and benzene).

Anal. Calcd. for C₁₁H₁₂N₂O₂S: C, 55.92; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.01; H, 5.15; N, 11.70; S, 13.60.

1-(2-Formamidomethylphenylsulfonyl)-1*H*-pyrrole (**14**).

A solution of **13** (0.5 g, 0.0021 mole) in ethyl formate (20 ml)

was refluxed for 1 hour, then the solvent was removed. The residue was chromatographed on an alumina column (ethyl acetate as eluent) to yield **14** (0.56 g, 100%), mp 60-61° (benzene-cyclohexane); ir: ν 3260 (NH) and 1650 cm^{-1} (C=O); ^1H -nmr (deuteriochloroform): δ 4.71 (d, 2H, $J = 6.6$ Hz, CH_2), 6.35 (m, 2H, pyrrole β -H), 6.53 (bs, 1H, NH), 7.13 (m, 2H, pyrrole α -H), 7.32-7.71 (m, 4H, benzene) and 8.15 (s, 1H, CH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.55; H, 4.48; N, 10.55; S, 12.20.

10*H*-Pyrrolo[1,2-*b*][1,2,5]benzothiadiazocine 5,5-Dioxide (**8**).

Formamido derivative **14** (1.0 g, 0.0038 mole) was dissolved in phosphorus oxychloride (20 ml) and the mixture was stirred at room temperature for 6 hours. Treatment with crushed ice (200 g), addition of sodium carbonate until pH 10 and extraction with chloroform (3 x 50 ml) gave a solution, which was dried and evaporated. The residue was chromatographed on an alumina column (ethyl acetate as eluent) to afford **8** (0.8 g, 86%), mp 128-130° (benzene-cyclohexane); ir: ν 1650 cm^{-1} (C=O); ^1H -nmr (deuteriochloroform): δ 4.94 (d, 2H, $J = 9.6$ Hz, CH_2), 6.32 (m, 1H, pyrrole β -H near imino group), 7.10-7.81 (m, 6H, pyrrole and benzene) and 8.18 (s, 1H, N=CH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.61; H, 4.01; N, 11.38; S, 13.00.

1-(2-Methoxycarbonylaminoethylphenylsulfonyl)-1*H*-pyrrole (**15**).

A solution of **13** (2.00 g, 0.0085 mole) and triethylamine (1.48 ml, 1.07 g, 0.0106 mole) in anhydrous tetrahydrofuran (90 ml), cooled to 0° was stirred for 10 minutes. Then a solution of methyl chlorocarbonate (0.68 ml, 0.83 g, 0.0089 mole) in anhydrous tetrahydrofuran (40 ml) was added dropwise and the mixture was stirred 15 minutes more at 0°. After filtration the solution was evaporated and the residue was treated with ethyl acetate (50 ml) and water (50 ml) and was shaken. The organic layer was separated, washed in turn with 1*N* hydrochloric acid (3 x 50 ml), saturated solution of sodium hydrogen carbonate (3 x 50 ml) and brine (3 x 50 ml). After drying and evaporation of the solvent, the residue was chromatographed on an alumina column (chloroform as eluent) to furnish **15** (0.73 g, 29%), mp 74-76° (benzene-cyclohexane); ir: ν 3400, 3300 (NH) and 1610 cm^{-1} (C=O); ^1H -nmr: δ 3.63 (s, 3H, CH_3), 4.61 (d, 2H, $J = 6.6$ Hz, CH_2), 5.45 (bs, 1H, NH), 6.34 (m, 2H, pyrrole β -H), 7.13 (m, 2H, pyrrole α -H) and 7.30-7.70 (m, 4H, benzene).

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 53.15; H, 4.81; N, 9.45; S, 10.83.

10*H*-Pyrrolo[1,2-*b*][1,2,5]benzothiadiazocin-12(11*H*)-one 5,5-Dioxide (**9**).

From **13**.

A solution of bis(trichloromethyl)carbonate (0.18 g, 0.0006 mole) in dichloromethane (4 ml) was dropped slowly onto a solution of **13** (0.4 g, 0.0018 mole) and triethylamine (0.25 ml, 0.18 g, 0.0018 mole) in the same solvent (9 ml). The solution was stirred at room temperature for 3 hours, then diluted with water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The extracts were collected, washed with brine (3 x 40 ml) and dried. Evaporation of the solvent gave a residue, which was purified by passing through an alumina column (ethyl acetate as eluent) to afford **9** (0.15 g, 32%), mp 161-163° (benzene); ir: ν 3320 cm^{-1} (NH); ^1H -

nmr (deuteriochloroform): δ 4.61 (d, 2H, $J = 6.4$ Hz, CH_2), 5.08 (t, 1H, $J = 6.4$ Hz, NH), 6.33 (m, 1H, pyrrole β -H), 7.03-7.65 (m, 6H, pyrrole α -H, β -H near the carbonyl and benzene).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: C, 54.95; H, 3.84; N, 10.68; S, 12.22. Found: C, 55.01; H, 3.81; N, 10.70; S, 12.15.

From **15**.

Zinc chloride (1.95 g, 0.014 mole) was melted at reduced pressure, cooled under nitrogen steam, then a solution of **15** (1.0 g, 0.0035 mole) in 1,2-dichlorobenzene (7 ml) was added and the mixture was refluxed for 5 hours. After treatment with water (10 ml) and extraction with ethyl acetate (3 x 10 ml) the organic solution was filtered on celite 577, dried and evaporated. The residue was chromatographed on an alumina column eluting with *n*-hexane until 1,2-dichlorobenzene was eliminated, then elution was continued with chloroform to yield **9** (0.17 g, 19%), identical with the sample obtained by the above method.

11-Methyl-10*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocin-12(11*H*)-one 5,5-Dioxide (**10**).

A mixture of **9** (0.27 g, 0.001 mole), iodomethane (0.25 ml, 0.57 g, 0.0031 mole) and anhydrous potassium carbonate (0.69 g, 0.005 mole) in anhydrous *N,N'*-dimethylformamide (10 ml) was heated to 90° for 16 hours while stirring. After cooling the mixture was poured onto crushed ice and then extracted with ethyl acetate (3 x 20 ml). The organic extracts were collected, washed with brine (3 x 40 ml) and dried. Removal of solvent gave a residue, which was purified by passing through an alumina column (chloroform as eluent) to afford **10** (0.07 g, 25%), mp 87-89° (benzene-cyclohexane); ir: ν 1630 cm^{-1} (C=O); ^1H -nmr (deuteriochloroform): δ 2.94 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.21-7.75 (m, 7H, pyrrole and benzene).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.50; H, 4.31; N, 10.18; S, 11.61.

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REFERENCES AND NOTES

- [1] K. D. Hargrave, J. R. Proudfoot, K. G. Grozinger, E. Cullen, S. R. Kapadia, U. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, M. L. Behnke, J. M. Klunder, K. Pal, J. W. Skiles, D. W. McNeil, J. M. Rose, G. C. Chow, M. T. Skoog, J. C. Wu, G. Schmidt, W. W. Engel, W. G. Eberlein, T. D. Saboe, S. J. Campbell, A. S. Rosenthal, and J. Adams, *J. Med. Chem.*, **34**, 2231 (1991).
- [2] V. J. Merluzzi, K. D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J. C. Wu, C.-K. Shih, K. Eckner, S. Hattox, J. Adams, A. S. Rosenthal, R. Faanes, R. J. Eckner, R. A. Koup, and J. L. Sullivan, *Science*, **250**, 1411 (1990).
- [3] R. Pauwels, K. Andries, J. Desmyter, D. Schols, M. J. Kukla, H. J. Breslin, A. Raeymaeckers, J. Van Gelder, R. Woestenborghs, J. Heykants, K. Schellekens, M. A. C. Janssen, E. De Clercq, and P. A. J. Janssen, *Nature*, **343**, 470 (1990).
- [4] M. J. Kukla, H. J. Breslin, R. Pauwels, C. L. Fedde, M. Miranda, M. K. Scott, R. G. Sherrill, A. Raeymaeckers, J. Van Gelder, K. Andries, M. A. C. Janssen, E. De Clercq, and P. A. J. Janssen, *J. Med. Chem.*, **34**, 746 (1991).
- [5] J. M. Klunder, K. D. Hargrave, M. A. West, E. Cullen, K.

Pal, M. L. Behnke, S. R. Kapadia, D. W. McNeil, J. C. Wu, G. C. Chow, and J. Adams, *J. Med. Chem.*, **35**, 1887 (1992).

[6] A. Chimirri, S. Grasso, A. M. Monforte, P. Monforte, and M. Zappalà, *Il Farmaco*, **46**, 925 (1991).

[7] M. Artico, G. Stefancich, R. Silvestri, S. Massa, E. Pagnozzi, A. G. Loi, D. Musu, M. Doa, P. Scano, and P. La Colla, *Med. Chem.*

Res., **4**, 283 (1994).

[8] M. Artico, R. Silvestri, E. Pagnozzi, G. Stefancich, S. Massa, A. G. Loi, P. Scano, S. Corrias, M. G. Spiga, and P. La Colla, unpublished results.

[9] R. Silvestri, E. Pagnozzi, M. Artico, G. Stefancich, S. Massa, and P. La Colla, *J. Heterocyclic Chem.*, in press.