Research on Nitrogen Containing Heterocyclic Compounds. XX. Synthesis of 8*H*-Imidazo[5,1-*c*]pyrrolo-[1,2-*a*][1,4]benzodiazepine and its 6-Derivatives

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Starting from 1*H*-1-(2-aminomethylphenyl)pyrrole the synthesis of 8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine, a novel nitrogen containing tetracyclic ring, has been performed by two routes involving a three-step and a six-step sequence, respectively. The more complex sequence offers the advantage to obtain also 3-alkyl and 3-aryl derivatives of the parent nucleus. The three step sequence involves the use of toluene-4-sulfonylmethylisocyanide (TosMIC) as a synthon.

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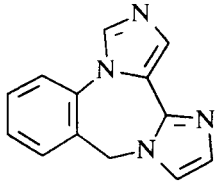
Our continued interest in nitrogen tetracyclic rings as potential pharmacophoric structures for drug design in the field of C.N.S. agents led us recently to synthesize novel 1,4-benzodiazepines annulated with two azole rings. Such tetracyclic systems have been widely studied by medicinal chemists due to the importance played by their derivatives as antianxiety, neuroleptic and antidepressant agents. The syntheses of 8*H*-diimidazo[1,5-*a*:2',1'-*c*][1,4]-benzodiazepine **1** [1], 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]-benzodiazepine **2** [2], 8*H*-imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]-benzodiazepine **3** [3], and 9*H*-pyrrolo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine **4** [4] have been described by us [1,4] and other authors [2,3] as effective approaches to the chemistry of novel tetracyclic nitrogen heterocycles of medicinal interest.



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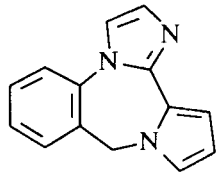

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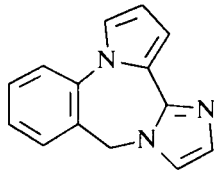

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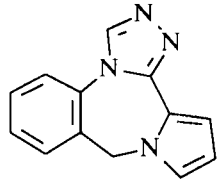

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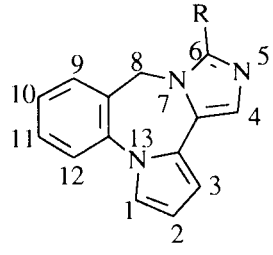


5a R = H

5b R = CH_3

5c R = C_6H_5

Following our searches in this area we describe now the synthesis of 8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine **5a** and some of its 6-derivatives **5b** and **5c**.

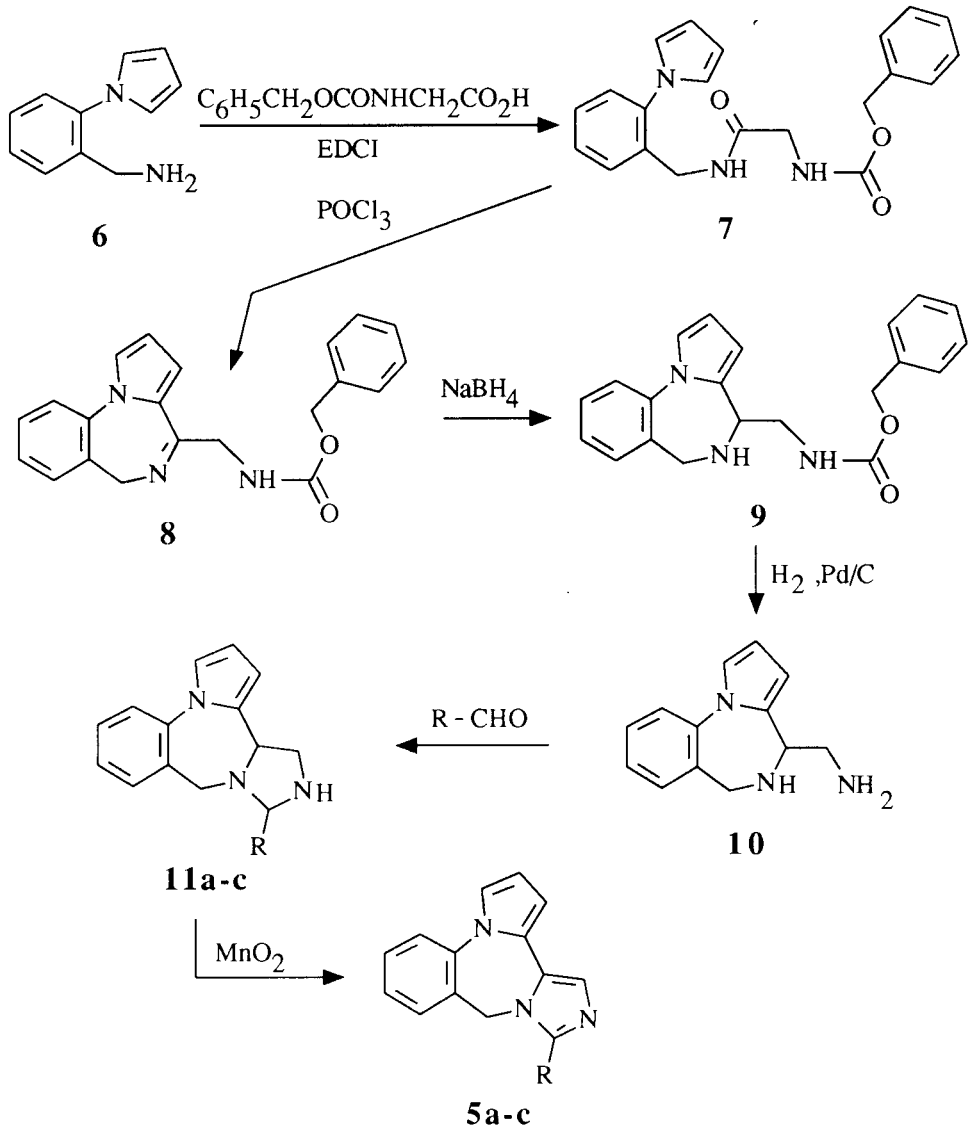
The synthesis of **5a** started from 1*H*-1-(2-aminomethylphenyl)pyrrole (**6**), which was reacted with *N*-benzyloxycarbonylglycine in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDCI) and triethylamine to give 1*H*-1-(2-benzyloxycarbonylaminoacetylaminomethylphenyl)pyrrole (**7**).

Intramolecular cyclization of **7** by the action of phosphorus oxychloride furnished the tricyclic pyrrolobenzodiazepine **8**, which was reduced by treatment with sodium borohydride to afford the aminoamide **9**. Removal of benzyloxycarbonyl group from this compound yielded 5,6-dihydro-4-aminomethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine **10**. The diamine **10** was then reacted with formaldehyde under Pictet-Spengler reaction conditions to give 3b,4,5,6-tetrahydro-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]-benzodiazepine **11a**. Similar reaction with acetaldehyde or with benzaldehyde afforded 3-methyl- (**11b**) and 3-phenyl-3b,4,5,6-tetrahydro-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]-benzodiazepine (**11c**), respectively.

Aromatization of imidazolidine ring by heating **11a-c** with manganese(IV) dioxide afforded the title compounds **5a-c** (Scheme 1).

The synthesis of the parent nucleus **5a** has been also obtained in a one-step reaction by 1,3-cycloaddition of toluene-4-sulfonylmethylisocyanide (TosMIC) [5] on the azomethine bond of 6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine **13**, a well known compound [6] easily obtainable from 1*H*-1-(2-formamidomethylphenyl)pyrrole **12**, which has been prepared by us starting from **6** [7] (Scheme 2). This very simple and expeditious reaction, however, does not allow the preparation of derivatives **5b** and **5c**.

Scheme 1

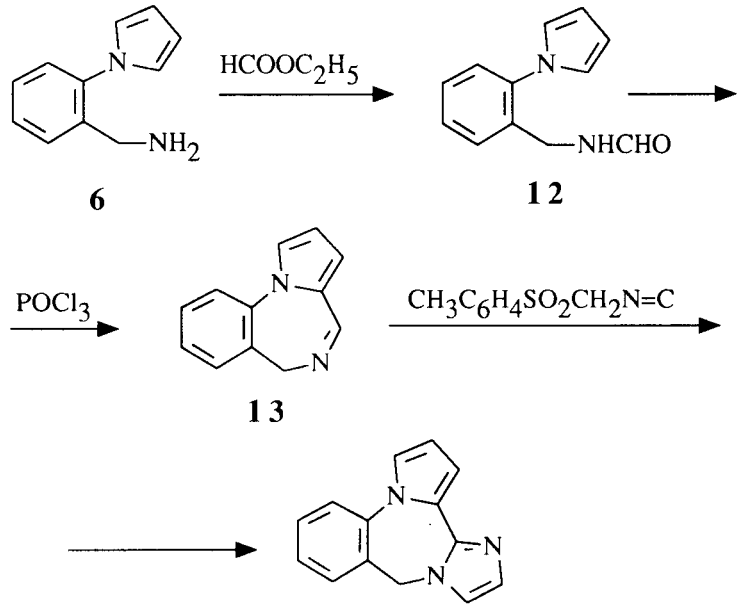


R = H (**5a**,**11a**), CH_3 (**5b**,**11b**), C_6H_5 (**5c**,**11c**).

EXPERIMENTAL

Melting points were determined on an Electrothermal IA6304 apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 1310 spectrophotometer in nujol mulls. The ^1H nmr spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as the internal standard. Column chromatography purifications were performed on alumina Merck (70-230 mesh). 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 sulphate. 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.

Scheme 2



1*H*-1-(2-Benzyloxycarbonylaminomethylphenyl)pyrrole (**7**).

N-Benzyloxycarbonylglycine (33.5 g, 0.160 mole), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) (33.7 g, 0.176 mole) and triethylamine (24.5 ml, 17.8 g, 0.176 mole) were added onto a cooled (0°), well-stirred solution of 1*H*-1-(2-aminomethylphenyl)pyrrole (**6**) (27.5 g, 0.160 mole) [7] in dichloromethane (150 ml). Then the mixture was stirred at room temperature for 2 hours. Stirring was continued at room temperature for 2 hours, then water was added (150 ml) and the mixture was extracted with chloroform (3 x 100 ml). The organic extracts were collected and washed with hydrochloric acid 1*N* (3 x 150 ml), brine (3 x 150 ml), saturated solution of sodium bicarbonate (3 x 150 ml), with brine again (3 x 150 ml) and dried. Removal of the solvent furnished **7** (58.1 g, 100%) which was used for the next reaction without further purification, mp 110-111° (from ethanol); ir: 3260 cm^{-1} (NH) and 1690, 1650 (CO groups); pmr (DMF-d_7): δ 3.87 (d, 2H, J_1 = 6 Hz, $COCH_2NHR$), 4.28 (d, 2H, J_2 = 6 Hz, $PhCH_2NHR$), 5.10 (s, 2H, OCH_2Ph), 6.27 (m, 2H, pyrrole β-H), 7.00 (m, 2H, pyrrole α-H), 7.31-7.63 (m, 9H, benzene) and 8.33 (s, broad, 2H, NH).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.35; H, 5.77; N, 11.68.

4-Benzyloxycarbonylaminomethyl-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**8**).

Compound **7** (2.2 g, 0.006 mole) was dissolved in phosphorus oxychloride (40 ml). The mixture was stirred at 40° for 4 hours, then evaporated. The residue was carefully treated with crushed ice (100 g) and sodium hydroxide 6*N* to *p*H 14. After extraction with chloroform (3 x 50 ml) the organic solution was washed with brine and dried. Removal of solvent furnished a residue (2.8 g) which was chromatographed on an alumina column (ethyl acetate as eluent) to give **8** (2.0 g, 100%), mp 72-76° (from benzene-cyclohexane); ir: 3360 cm^{-1} (NH), 1700 (C=O) and 1620 (C=N); pmr (deuteriochloroform): δ 4.27 (d, 2H, J = 4.5 Hz, $COCH_2NH$), 4.50 (d, 2H, $PhCH_2N$=), 5.10 (s, 2H, OCH_2Ph), 6.08 (s, broad, 1H, NH), 6.43 (m, 1H, pyrrole C_4-H), 6.77 (m, 1H, pyrrole C_3-H) and 7.27-7.53 (m, 10H, pyrrole C_5-H and benzene).

Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C, 73.02; H, 5.55; N, 12.17. Found: C, 72.99; H, 5.57; N, 12.25.

5,6-Dihydro-4-benzyloxycarbonylaminomethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**9**).

Sodium borohydride (1.1 g, 0.029 mole) was added to a well stirred solution of **8** (2.0 g, 0.060 mole) in 95% ethanol (30 ml). The mixture was stirred at room temperature for 20 hours, then the solvent was evaporated. The residue was treated with water (100 ml) and extracted with chloroform. The organic layer was separated, washed with brine and dried. After removal of solvent pure **9** (2.0 g, 96%) was obtained, mp 122-123° (from ethyl acetate); ir: 3290 and 3170 cm^{-1} (NH groups) and 1695 (C=O); pmr (DMF-d_7): δ 3.02 (s, broad, 1H, $PhCH_2NH$), 3.32-3.93 (m, 5H, $PhCH_2NH$, $CHCH_2NH$ and $CHCH_2$), 5.03 (s, 2H, OCH_2Ph), 6.25 (m, 2H, pyrrole β-H), 7.18 (m, 2H, pyrrole α-H and NHCOO) and 7.30-7.58 (m, 9H, benzene).

Anal. Calcd. for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.65; H, 6.15; N, 12.00.

5,6-Dihydro-4-aminomethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**10**).

Palladium on charcoal (10%, 75 mg) was added to a well stirred solution of **9** (0.5 g, 0.0015 mole) in glacial acetic acid (20

ml), then a solution of sodium hypophosphite hydrate (0.3 g, 0.0029 mole) in water (26.5 ml) was added dropwise. The mixture was refluxed for 1 hour, the catalyst was filtered and the solution was diluted with water, treated with sodium hydroxide 2*N* to *p*H 14, then extracted with ethyl acetate. The extracts were collected, washed with brine, dried and evaporated to give **10** (250 mg, 78%), mp 155-157° (from benzene/cyclohexane); ir: 3260 and 3190 cm^{-1} (NH and NH_2); pmr (deuteriochloroform): δ 2.87 (s, broad, 2H, NH_2), 3.42-4.02 (m, 5H, $PhCH_2NH$, $CHCH_2NH_2$ and $CHCH_2$), 6.17-6.52 (m, 3H, pyrrole β-H and NH), 6.98 (m, 1H, pyrrole α-H) and 7.23-7.48 (m, 4H, benzene).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.08; N, 19.70. Found: C, 73.11; H, 7.10; N, 19.76.

3b,4,5,6-Tetrahydro-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**11a**).

Formaldehyde (37%, 0.1 ml, 0.0014 mole) was added to a solution of **10** (100 mg, 0.00047 mole) in methanol (4 ml). The mixture was stirred at 60° for 16 hours. After this time the mixture was concentrated and treated with ethyl acetate (20 ml). The organic layer was separated, washed with brine, dried and the solvent was evaporated. The crude product was chromatographed on an alumina column (ethyl acetate as eluent) giving pure **11a** (40 mg, 38%) as a yellowish oil; ir: 3400 cm^{-1} (NH); pmr (deuteriochloroform): δ 2.58 (s, broad, 1H, NH), 3.08-4.70 (m, 7H, $PhCH_2N$, NCH_2NH, $CHCH_2$ and $CHCH_2$), 6.18-6.37 (m, 2H, pyrrole β-H), 7.03 (m, 1H, pyrrole α-H) and 7.28-7.55 (m, 4H, benzene).

Anal. Calcd. for $C_{14}H_{15}N_3$: C, 74.63; H, 6.71; N, 18.65. Found: C, 74.55; H, 6.88; N, 18.77.

6-Methyl-3b,4,5,6-tetrahydro-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]-benzodiazepine (**11b**).

Acetaldehyde (0.4 ml, 0.007 mole) was added onto a solution of **10** (500 mg, 0.0023 mole) in methanol (20 ml). The mixture was refluxed for 30 minutes, then the solvent was evaporated and the residue was chromatographed on an alumina column (ethyl acetate as eluent). Removal of solvent from collected eluates afforded **11b** (40 mg, 79%) as a yellowish oil; ir: 3400 cm^{-1} (NH); pmr (deuteriochloroform): δ 1.38 (m, 3H, CH_3), 1.88 (s, broad, 1H, NH), 3.57-4.30 (m, 5H, $PhCH_2$, $CHCH_2$ and $CHCH_2$), 4.92 (q, 1H, J = 6 Hz, $CHCH_3$), 6.17-6.38 (m, 2H, pyrrole β-H), 7.05 (m, 1H, pyrrole α-H) and 7.25-7.55 (m, 4H, benzene).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.33; H, 7.11; N, 17.50.

6-Phenyl-3b,4,5,6-tetrahydro-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]-benzodiazepine (**11c**).

Prepared starting from diamine **10** (0.0023 mole) and benzaldehyde as reported for **11b** by heating at reflux for 15 hours. Chromatography on alumina column (chloroform as eluent) furnished pure **11c** (430 mg, 60.7%) as a yellowish oil; ir: 3280 cm^{-1} (NH); pmr (deuteriochloroform): δ 2.35 (s, broad, 1H, NH), 3.31-4.39 (m, 5H, $PhCH_2N$, $CHCH_2$ and $CHCH_2$), 5.24 and 5.33 (2s, 1H, $CHPh$), 6.31 (m, 2H, pyrrole β-H), 7.04 (m, 1H, pyrrole α-H) and 7.24-7.61 (m, 9H, benzene).

Anal. Calcd. for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.71; H, 6.43; N, 14.01.

8*H*-Imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**5a**).

Method A.

Manganese(IV) oxide (1.4 g, 0.016 mole) was added to a solution of **11a** (180 mg, 0.0008 mole) in anhydrous benzene (20 ml). The mixture was refluxed 16 hours, then the solid was filtered and washed with chloroform. The filtrate was evaporated to give a crude product which was chromatographed on an alumina column (ethyl acetate as eluent) to yield **5a** (25 mg, 14%), mp 189-191° (from ethyl acetate); pmr (deuteriochloroform): δ 4.98 (s, 2H, CH_2), 6.38-6.60 (m, 2H, pyrrole β-H), 7.13-7.48 (m, 6H, pyrrole α-H, imidazole C_4-H and benzene) and 7.55 (s, 1H, imidazole C_2-H).

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.98; H, 5.03; N, 18.87.

Method B.

A solution of toluene-4-sulfonylmethylisocyanide (940 mg, 0.0048 mole) in anhydrous tetrahydrofuran (10 ml) was added, under nitrogen atmosphere, to a cooled (−50°) well-stirred solution of *n*-butyllithium (1.6 *M* in *n*-hexane, 6.1 ml, 0.0096 mole) in anhydrous tetrahydrofuran (20 ml). To this solution compound **13** (800 mg, 0.0044 mole) dissolved in anhydrous tetrahydrofuran (100 ml) was added dropwise. The mixture was stirred at −50° for 30 minutes and then at room temperature for 36 hours. After treatment with water (50 ml) and extraction with ethyl acetate, the organic solution was washed with brine, dried on anhydrous sodium sulphate and the solvent was evaporated. The crude product was chromatographed on an alumina column (ethyl acetate as eluent) to yield **5a** (590 mg, 61%) identical to the sample obtained with method A.

6-Methyl-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**5b**).

Compound **5b** was prepared from imidazolidine **11b** (0.0008 mole) as reported for **5a** (method A, refluxing time 5 hours); **5b** (80 mg, 43%) had mp 183° dec after recrystallization from ethyl acetate; pmr: δ 2.5 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 6.32-6.58 (m, 2H, pyrrole β-H) and 7.02-7.68 (m, 6H, pyrrole α-H, imidazole and benzene).

Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.69; H, 5.47; N, 17.87.

6-Phenyl-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**5c**).

Compound **5c** was obtained as a yellowish oil (40 mg, 17%) starting from **11c** (0.0008 mole) as reported for **5a** (method A); pmr (deuteriochloroform): δ 5.05 (s, 2H, CH_2), 6.45 and 6.58 (m, 2H, pyrrole β-H) and 6.98-7.78 (m, 11H, pyrrole α-H, imidazole and benzene).

Anal. Calcd. for $C_{20}H_{15}N_3$: C, 80.78; H, 5.09; N, 14.13. Found: C, 80.77; H, 5.00; N, 14.11.

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

A solution of **6** (5.4 g, 0.031 mole) [7] in ethyl formate (50 ml) was refluxed for 18 hours, then the solvent was removed. The crude product was chromatographed on an alumina column (ethyl acetate as eluent) to give **12** (4.7 g, 73%), mp 98-101° (from ethyl acetate); ir: 3180 cm^{-1} (NH) and 1645 (C=O); pmr (deuteriochloroform): δ 4.33 (d, 2H, J = 6 Hz, CH_2), 5.75 (s, broad, 1H, NH), 6.32 (m, 2H, pyrrole β-H), 6.77 (m, 2H, pyrrole α-H), 7.25-7.58 (m, 4H, benzene) and 8.08 (s, 1H, CH).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.05; H, 6.01; N, 14.05.

1*H*-Pyrrolo[1,2-*a*][1,4]benzodiazepine (**13**).

Compound **13** was prepared starting from **12** (0.005 mole) as reported for **8** [6].

Acknowledgements.

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