Research on Nitrogen Containing Heterocyclic Compounds; XIV. Derivatives of 5*H*-Pyrrolo[1,2-*b*][1,2,5]benzotriazepine, a Novel Tricyclic Ring System, by Intramolecular Cyclization of *N*-Aryl-1*H*-pyrrol-1-amines

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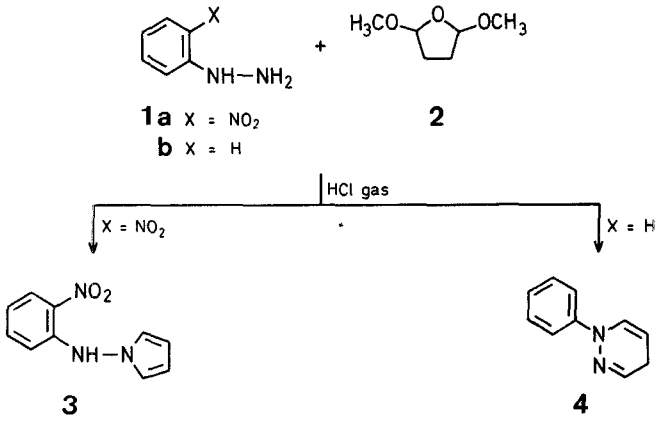
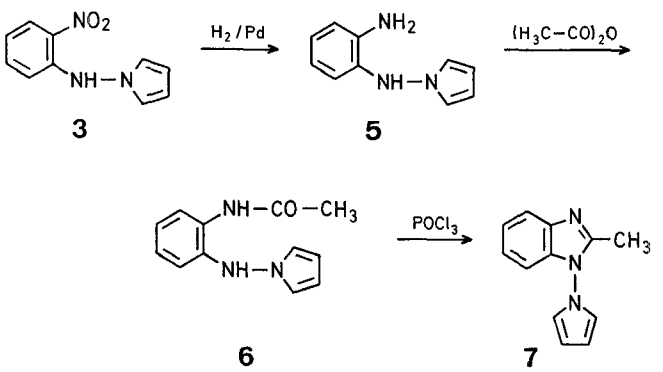
Antitumoral activities of pyrrolobenzodiazepine antibiotics[1] and the useful therapeutical action on the central nervous system shown by some tricyclic derivatives possessing the benzodiazepine skeleton[2] have focused the attention of chemists on the synthesis of new tricyclic ring systems with a bridgehead nitrogen atom.

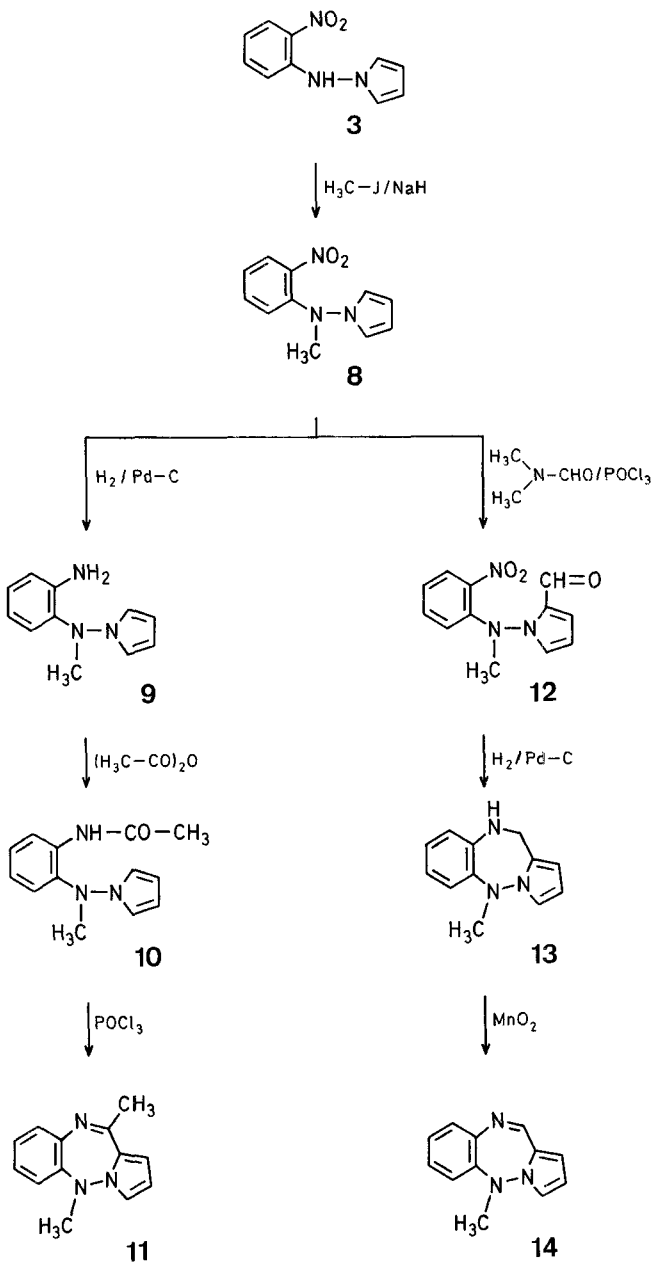
We have previously synthesized various novel benzoazepine, benzodiazepine, benzoxazepine and benzothiadiazepine nuclei fused with a pyrrole or imidazole moiety[3]. To our knowledge, the 5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine system was previously unknown. The present work is concerned with the synthesis of some derivatives of this novel kind of 6,7,5-membered tricyclic heteroaromatic system. As starting material, we chose *N*-(2-nitrophenyl)-amino-1*H*-pyrrole **(3)** which has been prepared in good yield by treating 2-nitrophenylhydrazine **(1a)** with 2,5-dimethoxytetrahydrofuran **(2)** in absolute ethanol saturated with gaseous hydrochloric acid. We observed that a similar reaction starting from phenylhydrazine **(1b)** led to the *N*-phenyldihydropyridazine **4**[4] as the only product. On the other hand, the formation of **3** did not occur when the above reaction was carried out in glacial acetic acid[5], the known 2-nitrophenylhydrazide of acetic acid being the only product formed.



Unfortunately, **3** could not be used directly to prepare the title 5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine derivatives. In fact, *N*-(2-acetylaminophenyl)-1*H*-pyrrol-1-amine **(6)**, prepared by the action of acetic anhydride on the amino derivative **5**, which is formed by reducing **3** with hydrogen in the presence of 10% palladium on carbon as catalyst, when treated with phosphoryl chloride cyclized intramolecularly to 1-(1-pyrryl)-2-methylimidazole **(7)**. The structure of this compound deduced from its ^{1}H-N.M.R. spectrum.



However, we were successful by introducing a methyl group at the NH-position of **3**. The new derivative **8**, on catalytic reduction followed by acetylation, furnished the key compound *N*-(2-acetylaminophenyl)-*N*-methyl-1*H*-pyrrol-1-amine **(10)**. This compound, when subjected to intramolecular cyclization by treatment with phosphoryl chloride afforded the expected 5,11-dimethyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **(11)**. Furthermore, Vilsmeier-Haack formylation of **8** and subsequent catalytic reduction of the formed *N*-methyl-*N*-(2-nitrophenyl)-2-formyl-1*H*-pyrrol-1-amine **(12)** led to 5-methyl-10,11-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **(13)**. Oxidation with activated manganese dioxide of **13** gave 5-methyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **(14)**.



All compounds here reported were characterized by I.R. spectra, microanalysis and, sometimes, by mass spectra; ^{1}H-N.M.R. spectra of compounds **11**, **13**, and **14** were consistent with their tricyclic structures. Derivatives **3** and **7**, in a preliminary screening, showed promising antibacterial activities.

All melting points were measured with a Fisher-Johns apparatus and are uncorrected. I.R. spectra (nujol mulls) were recorded on a Perkin-Elmer model 297 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Varian EM-390 instrument (T.M.S. internal standard). The mass spectra were recorded on a Hewlett-Packard 5908-A mass spectrometer with an electron beam energy of 70 eV. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

_N_-(2-Nitrophenyl)-1_H_-pyrrol-1-amine (3):
A stirred suspension of 2-nitrophenylhydrazine (**1a**; 15.3 g, 0.1 mol) in absolute ethanol (300 ml) is heated under reflux and gaseous hydrochloric acid is bubbled through until saturation is complete. A solution of 2,5-dimethoxytetrahydrofuran (**2**; 14.5 g, 0.11 mol) in absolute ethanol (50 ml) is then added and the mixture is heated under reflux for 30 min. The precipitate obtained after treatment of the reaction mixture with crushed ice (600 g) and solid sodium hydrogen carbonate (160 g) is filtered, then dissolved in benzene (150 ml) and the solution is passed through a silica gel column, eluting with benzene. Evaporation of the solvent from the eluates furnishes _N_-(2-nitrophenyl)-1_H_-pyrrol-1-amine **(3)**; yield: 16 g (79%); m.p. 114–117 °C (after recrystallization from ligroin).

$C_{10}H_9N_3O_2$	calc.	C 59.10	H 4.46	N 20.68
(203.2)	found	59.38	4.67	20.47

I.R.: $\nu = 3350$ cm^{-1} (NH).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.25$ (m, 2H); 6.8 (m, 2H); 7.2–8.4 (3m, 4H); 9.95 ppm (br. s, 1H).

_N_-(2-Aminophenyl)-1_H_-pyrrol-1-amine (5):
To a solution of **3** (4.06 g, 20 mmol) in ethyl acetate (100 ml), 10% palladium on carbon (200 mg) is added and the mixture is hydrogenated at room temperature under 4 atmospheres of hydrogen for 4 h. Removal of the catalyst by filtration and evaporation of the solvent under reduced pressure on a steam-bath affords _N_-(2-aminophenyl)-1_H_-pyrrol-1-amine as an oil, which after distillation in vacuo becomes solid; yield: 2.8 g (81%); b.p. 130–132 °C/0.15–0.18 torr; m.p. 67–70 °C (after crystallization from cyclohexane).

$C_{10}H_{11}N_3$	calc.	C 69.34	H 6.40	N 24.26
(173.2)	found	69.07	6.13	24.03

I.R.: $\nu = 3400$, 3300 and 3250 cm^{-1} (NH_2 and NH).

M.S.: $m/e = 173$ (M^+).

_N_-(2-Acetylaminophenyl)-1_H_-pyrrol-1-amine (6):
Acetyl chloride (1.0 g, 10 mmol) in anhydrous tetrahydrofuran (25 ml) is dropped while stirring into an ice-cooled solution of **5** (1.73 g, 10 mmol) and triethylamine (1.0 g, 10 mmol) in the same solvent (50 ml). The resulting mixture is kept at room temperature for 1 h, then filtered and evaporated under reduced pressure. The solid residue after crystallization from aqueous ethanol gives _N_-(2-acetylaminophenyl)-1_H_-pyrrol-1-amine **(6)**; yield: 1.8 g (84%); m.p. 172–174 °C.

$C_{12}H_{13}N_3O$	calc.	C 66.95	H 6.09	N 19.52
(215.3)	found	67.13	6.32	19.35

I.R.: $\nu = 3250$–3300 cm^{-1} (NH), 1650 cm^{-1} (CO).

1-(1-Pyrryl)-2-methylbenzimidazole (7):
A mixture of **6** (2.15 g, 10 mmol) and phosphoryl chloride (15 ml) is heated under reflux for 30 min, then poured on to crushed ice (100 g) and made alkaline by adding concentrated ammonia. Extraction with ethyl acetate (150 ml) followed by drying with anhydrous sodium sulphate, filtration, and evaporation of the solvent gives a residue which is chromatographed on an alumina column eluting with chloroform. The first eluates are collected and evaporated in vacuo to give 1-(1-pyrryl)-2-methylbenzimidazole **(7)**; yield: 1.57 g (80%); m.p. 142–144 °C after crystallization from aqueous ethanol.

$C_{12}H_{11}N_3$	calc.	C 73.07	H 5.62	N 21.31
(197.2)	found	73.29	5.40	21.07

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.40$ (s, 3H); 6.4, 6.85 (m, 4H); 6.9–7.8 ppm (m, 4H).

M.S.: $m/e = 197.3$ (M^+).

_N_-Methyl-_N_-(2-nitrophenyl)-1_H_-pyrrol-1-amine (8):
A solution of **3** (10.16 g, 0.05 mol) and an equimolar amount of iodomethane in anhydrous tetrahydrofuran (50 ml) is added to a suspension of sodium hydride (3.0 g, 0.1 mol, 80% suspension) in the same solvent (200 ml). The mixture is heated to 80 °C under stirring for 18 h, then ethanol (5 ml) is added to destroy the excess hydride. After removal of the solvents on a steam bath under reduced pressure the residue is treated with crushed ice (400 g) and concentrated hydrochloric acid (10 ml). Extraction with chloroform (200 ml) followed by drying with anhydrous sodium sulphate, and evaporation of solvent furnishes on oily residue, which is subjected to chromatographic purification on a silica gel column, eluting with benzene. The eluates are collected and evaporated to give _N_-methyl-_N_-(2-nitrophenyl)-1_H_-pyrrol-1-amine **(8)**; yield: 10.2 g (98%); m.p. 85–89 °C (after recrystallization from light petroleum ether).

$C_{11}H_{11}N_3O_2$	calc.	C 60.82	H 5.10	N 19.35
(217.2)	found	60.98	5.37	19.13

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.30$ (s, 3H); 6.2 (m, 2H); 6.8 (m, 2H); 6.9–7.8 ppm (m, 4H).

_N_-(2-Aminophenyl)-_N_-methyl-1_H_-pyrrol-1-amine (9):
A solution of **8** (4.34 g, 0.02 mol) in benzene (100 ml) containing 10%

palladium on carbon (200 mg) is hydrogenated at room temperature under 4 atmospheres of pressure for 4 h. Removal of the catalyst by filtration and evaporation of solvent in vacuo furnishes the oily *N*-(2-aminophenyl)-*N*-methyl-1*H*-pyrrol-1-amine **(9)**, which is purified by distillation; yield: 3.6 g (96%); b.p. 140–143 °C/0.55–0.6 torr.

$C_{11}H_{13}N_3$	calc.	C 70.56	H 7.00	N 22.44
(187.2)	found	70.37	6.83	22.16

I.R.: $\nu = 3450$ and 3330 cm^{-1} (NH_2).

^{1}H-N.M.R. (CCl_4): $\delta = 3.10$ (s, 3H); 3.63 (s, 2H, disappears on treatment with D_2O); 6.0 (m, 2H); 6.4–7.5 ppm (m, 6H).

N-(2-Acetylaminophenyl)-N-methyl-1H-pyrrol-1-amine (10):
A solution of **9** (3.74 g, 0.02 mol) in benzene (100 ml) is treated with triethylamine (2.0 g, 0.02 mol) and cooled on ice-bath. Then a solution of acetyl chloride (1.57 g, 0.02 mol) in benzene (25 ml) is dropped into while stirring. The mixture is left at room temperature for 1 h, then filtered, and evaporated in vacuo. The residue is dissolved in chloroform (20 ml) and chromatographed on a silica gel column by elution with the same solvent. The central eluates are collected and evaporated under reduced pressure to give *N*-(2-acetylaminophenyl)-*N*-methyl-1*H*-pyrrol-1-amine **(10)**, yield: 3.9 g (85%); b.p. 185–188 °C/1 torr.

$C_{13}H_{15}N_3O$	calc.	C 68.10	H 6.89	N 18.33
(229.3)	found	68.21	6.98	18.05

I.R.: $\nu = 3400$ cm^{-1} (NH) and 1690 cm^{-1} (CO).

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.05$ (s, 3H); 3.2 (m, 3H); 6.0 (m, 2H); 7.0–8.0 (m, 6H); 9.1 ppm (s, 1H).

5,11-Dimethyl-5H-pyrrolo[1,2-b][1,2,5]benzotriazepine (11):
A mixture of **10** (6.88 g, 0.03 mol) and phosphoryl chloride (20 ml) is heated under reflux for 0.5 h, then evaporated under reduced pressure and the residue is treated with crushed ice (400 g) and concentrated ammonium hydroxide solution (20 ml). After extraction with ethyl acetate (200 ml), the organic solution is dried with anhydrous sodium sulphate and evaporated. The crude residue is dissolved in benzene (35 ml) and chromatographed over an alumina column eluting with the same solvent. The eluates are collected and evaporated to give 5,11-dimethyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **(11)**; yield: 5.7 g (95%); b.p. 234–235 °C/0.6 torr. On standing compound **11** solidifies; m.p. 75–76 °C (after crystallization from cyclohexane).

$C_{13}H_{13}N_3$	calc.	C 73.90	H 6.20	N 19.89
(211.3)	found	73.64	6.01	19.68

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.50$ (s, 3H); 3.00 (s, 3H); 6.15, 6.65, 6.7 (3m, 3H); 7.2–7.5 ppm (m, 4H).

M.S.: $m/e = 211$ (M^+).

N-Methyl-N-(2-nitrophenyl)-2-formyl-1H-pyrrol-1-amine (12):
Phosphoryl chloride (15.3 g, 0.1 mol) is dropped under stirring into *N,N*-dimethylformamide (7.3 g, 0.1 mol) cooled to 0–5 °C. After adding, the mixture is stirred for 15 min more, then treated with a solution of **8** (10.86 g, 0.05 mol) in dimethylformamide (30 ml) and heated to 110–120 °C for 2.5 h. Treatment with concentrated ammonia solution (60 ml) and crushed ice (450 g) gives a precipitate which, after filtration, is dissolved in benzene (50 ml) and passed through a silica gel column, eluting with the same solvent. The collected eluates are evaporated under reduced pressure to afford *N*-methyl-*N*-(2-nitrophenyl)-2-formyl-1*H*-pyrrol-1-amine **(12)**; yield: 8.7 g (71%); m.p. 74–75 °C [after recrystallization from benzene/petroleum ether (1:1)].

$C_{12}H_{11}N_3O_3$	calc.	C 58.77	H 4.52	N 17.14
(245.2)	found	58.93	4.66	17.21

I.R.: $\nu = 1680$ cm^{-1} (CHO).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.35$ (s, 3H); 6.3 (m, 1H); 6.8–7.7 (m, 6H); 9.60 ppm (s, 1H).

5-Methyl-10,11-dihydro-5H-pyrrolo[1,2-b][1,2,5]benzotriazepine (13):
A suspension of **12** (7.35 g, 0.03 mol) and 10% palladium on carbon (500 mg) in ethyl acetate (200 ml) is hydrogenated at 50 °C under 4 atmospheres of hydrogen for 4 h. Removal of the catalyst by filtration and subsequent evaporation of the solvent under reduced pressure on a steam-bath affords crude **13** (5.8 g), which is purified by distillation in vacuo; yield: 3.0 g (50%); b.p. 169–173 °C/0.75–0.8 torr. On standing 5-methyl-10,11-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine solidifies; m.p. 62–64 °C (after crystallization from cyclohexane).

$C_{12}H_{13}N_3$	calc.	C 72.33	H 6.57	N 21.09
(199.3)	found	72.53	6.65	21.07

I.R.: $\nu = 3400$ cm^{-1} (NH).

^{1}H-N.M.R. (CCl_4): $\delta = 3.20$ (s, 3H); 3.70 (t, 1H, disappears on treatment with D_2O); 4.10 (s, 2H); 5.7 (m, 2H); 6.15 (m, 1H); 6.3–7.3 ppm (m, 4H).

M.S.: $m/e = 199$ (M^+).

5-Methyl-5H-pyrrolo[1,2-b][1,2,5]benzotriazepine (14):
Manganese dioxide[6] (5.0 g) is added to a solution of **13** (996 mg, 0.005 mol) in acetone (200 ml). The mixture is stirred overnight then filtered and the inorganic material is washed twice with acetone on the filter. After evaporation, the organic filtrate furnishes a crude oil (900 mg), which is distilled under reduced pressure to afford the oily 5-methyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **(14)**; yield: 800 mg (81%); b.p. 108 °C/0.05 torr.

$C_{12}H_{11}N_3$	calc.	C 73.07	H 5.62	N 21.31
(197.2)	found	72.87	5.78	21.00

^{1}H-N.M.R. (CCl_4): $\delta = 2.9$ (s, 3H); 6.0, 6.35, 6.9 (3m, 3H); 7.1–7.5 (m, 4H); 8.20 ppm (s, 1H).

M.S.: $m/e = 197$ (M^+).

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