Research on Nitrogen Containing Heterocyclic Compounds. XVIII. Synthesis of 9*H*-Pyrrolo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, a Novel Tetracyclic Ring of Pharmaceutical Interest

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Reaction of di-4-morpholinylphosphinic chloride on 5,10-dihydro-9*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one **9** afforded 11-(di-4-morpholinylphosphinyloxy)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **10**. Displacement of di-4-morpholinylphosphinyloxy group of **10** by formylhydrazine with concomitant intramolecular cyclization led directly to 9*H*-pyrrolo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine **7**, a novel nitrogen heterocyclic ring of pharmaceutical interest. A new procedure for the synthesis of **9** is also described.

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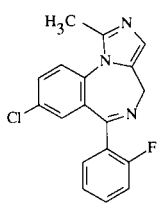
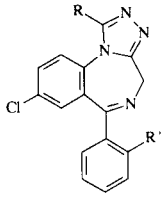
Tricyclic benzodiazepines containing imidazole and triazole, *e.g.* midazolam **1**, estazolam and its analogs **2**, are well-known as psychotropic agents. In the last few years tetracyclic benzodiazepines also have received great attention. Among these substances bretazenil **3** is actually undergoing pharmacological screening as an anxiolytic agent [1]. The importance of the tetracyclic moiety as pharmacophoric support for displaying CNS activities is well documented by aptazepine **4**, a potent antidepressant agent with clinical applications [2].



1 midazolam



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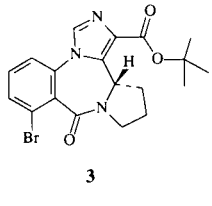
R = H; R' = H estazolam
R = CH ; R' = H alprazolam
R = CH ; R' = Cl triazolam



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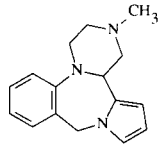
As a result of our decennial engagement in the area of nitrogen-containing heterocyclic compounds we have reported the synthesis of 10-methyl-10-azaaptazepine **5** as a new potential antidepressant agent [3] and, more recently, we realized the synthesis of 8*H*-diimidazo[1,5-*a*:2',1'-*c*]-[1,4]benzodiazepine **6** [4], strictly related to the tetracyclic structure of bretazenil **3**.

In this paper we wish to present the synthesis of 9*H*-pyrrolo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine **7**, a novel nitrogen heterocyclic ring containing both the pyrrolo[2,1-*c*][1,4]benzodiazepine moiety present in the aptazepine structure **4** and the *s*-triazolo[4,3-*a*][1,4]benzodiazepine skeleton of compounds **2**.



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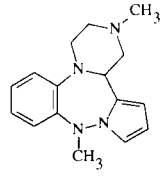

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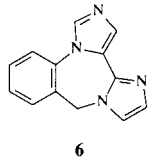

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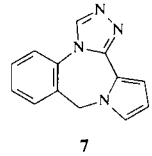
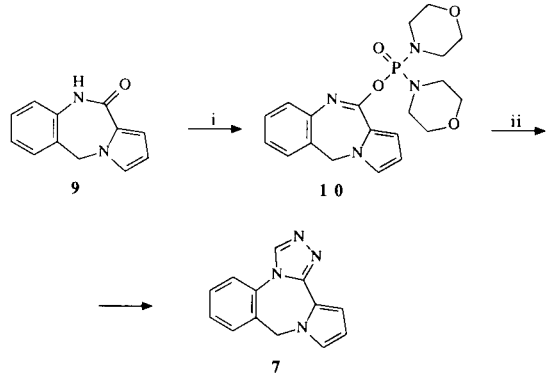


7

The key step for the synthesis of **7** was the preparation of intermediate 11-(di-4-morpholinylphosphinyloxy)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **10** by phosphorylation with di-4-morpholinylphosphinic chloride of 5,10-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one **9** (Scheme 1). The di-4-morpholinylphosphinyloxy imine **10** in fact reacted promptly with formylhydrazine to give directly **7**, by displacement of the di-4-morpholinylphosphinyloxy group and subsequent ring closure.

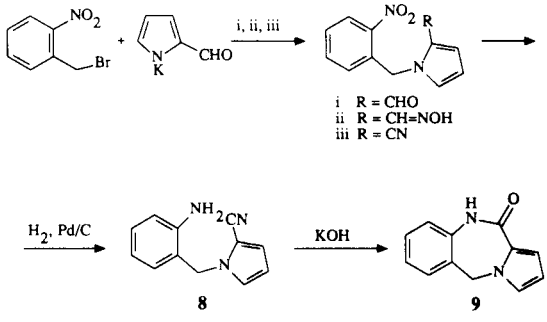
Scheme 1



9 **10** **7**

Preparation of lactam **9** has been first reported by Artico [5], through a five-step procedure starting from 2-nitrobenzyl bromide and 2-pyrrolecarboxyaldehyde (Scheme 2). The last step of this procedure involved the one-pot conversion of 1-(2-aminobenzyl)-2-cyanopyrrole **8** into **9** by heating the nitrile at 180° in potassium hydroxide/diethylene glycol.

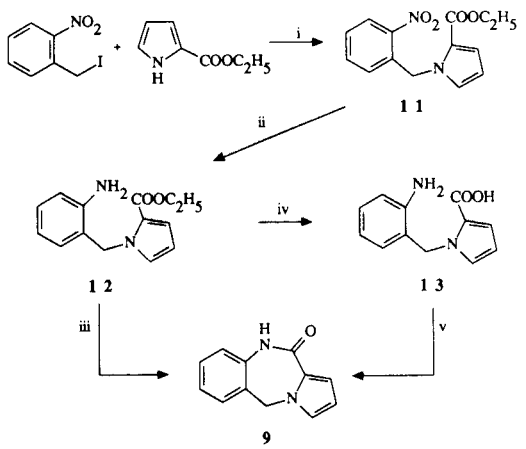
Scheme 2



In his attempts to follow this procedure for the one-step conversion of 1-(2-aminobenzyl)-2-pyrrolecarbonitrile Wright [6] obtained 1-(2-aminobenzyl)-2-pyrrolecarboxylic acid **13** as the major product, which could be then converted to **9** by treatment with *N,N*-carbonyldiimidazole (CDI) (one additional step).

In the present work we used for the synthesis of **9** a three-step procedure based on the reaction of 2-nitrobenzyl iodide [7] with ethyl 2-pyrrolecarboxylate [8] in the presence of potassium *tert*-butoxide and 18-crown-6 (Scheme 3). The formed nitroester **11** was reduced with hydrogen in the presence of 10% palladium on charcoal to aminoester **12**, which was converted to **9** by heating in the presence of 2-hydroxypyridine as a bi-functional catalyst (total yield 62%).

Scheme 3



i: potassium *tert* -butoxide. ii: hydrogen - Pd/C. iii: 2-hydroxypyridine, Δ. iv: potassium hydroxide, ethanol. v: 1,1'-carbonyldiimidazole, THF.

Alternatively, **12** was easily hydrolyzed with potassium hydroxide in ethanol to the corresponding aminoacid **13**, which was then cyclized to **9** by treatment with *N,N'*-carbonyldiimidazole, as described by Wright [8].

EXPERIMENTAL

Melting points were determined by an Electrothermal IA 6304 apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 1310 spectrophotometer. The pmr spectra (deuteriochloroform) were recorded on Varian EM-390 spectrometer with TMS as internal standard. Merck alumina and Merck silica gel (70-230 mesh ASTM) were used for chromatographic purifications. Carlo Erba Stratocrom SIF and Stratocrom ALF precoated plates were used for thin-layer chromatography. Microanalyses were performed by A. Pietrogrande, Padova, Italy. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvents involved the use of a rotary evaporator operating at reduced pressure.

Ethyl 1-(2-Nitrobenzyl)-2-pyrrolecarboxylate (**11**).

A solution of ethyl 2-pyrrolecarboxylate (3.2 g, 23 mmoles) in dry tetrahydrofuran (55 ml) was added dropwise to a well-stirred mixture of 18-crown-6 (0.6 g, 23 mmoles) and potassium *tert*-butoxide (2.58 g, 23 mmoles) in the same solvent (55 ml). After 15 minutes, a solution of 2-nitrobenzyl iodide (6.4 g, 2.3 mmoles) in dry tetrahydrofuran (55 ml) was slowly added into the ice-cooled suspension and stirring was maintained for 2.5 hours at room temperature. After concentration, water and dichloromethane were added and the organic layer was separated, washed with brine and dried. Removal of the solvent furnished a residue which was purified on silica gel column eluting with chloroform-petroleum ether (1:1). The central eluates were collected and evaporated to give **11** (4.79 g, 76%), mp 82-84° after recrystallization from cyclohexane; pmr: δ 1.17 (t, 3H), 4.13 (q, 2H), 5.93 (s, 2H), 6.27 (m, 1H), 6.38-6.55 (m, 1H), 6.93 (m, 1H), 7.10 (m, 1H), 7.28-7.65 (m, 2H), 8.08-8.28 ppm (m, 1H).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.07; H, 4.98; N, 10.45.

Ethyl 1-(2-Aminobenzyl)-2-pyrrolecarboxylate (**12**).

A solution of **11** (3.01 g, 11 mmoles) in 200 ml of ethyl acetate-ethanol (9:1) containing 10% palladium on charcoal (400 mg) was hydrogenated in a Parr apparatus for 3 hours at 45° and 50 psi of pressure. Removal of the catalyst by filtration and evaporation of the solvent furnished **12** (2.57 g, 96%), mp 51-52° after recrystallization from ethanol-water; pmr: δ 1.28 (t, 3H), 3.92 (s, disappeared on treating with deuterium oxide, 2H), 4.27 (q, 2H), 5.45 (s, 2H), 6.13 (m, 1H), 6.58-7.28 ppm (m, 6H).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.75; H, 6.62; N, 11.43.

1-(2-Aminobenzyl)-2-pyrrolecarboxylic Acid (**13**).

A mixture of **12** (2.44 g, 10 mmoles), potassium hydroxide (1.68 g, 30 mmoles) and ethanol (6.3 ml) was refluxed for 1 hour. After removal of the solvent, the residue was treated with crushed ice, then acidified by adding 37% hydrochloric acid until *p*H 2. After extraction with ethyl acetate, the organic solution was washed with brine, dried and evaporated to give **13** (1.5 g, 69%), mp 139-141° (lit [6] mp 141-142°), which was used for the cyclization without further purification.

5,10-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**9**).

A mixture of **12** (1.65 g, 6.7 mmoles) and 2-hydroxypyridine (0.63 g, 6.7 mmoles) was well stirred under nitrogen for 48 hours, while heating at 170°. After cooling, the residue was purified on an alumina column eluting with chloroform. The first fractions containing traces of **12** were discarded and the second eluates furnished **9** (1.09 g, 82%), mp 220-223° after recrystallization from ethanol (lit [5b,6] mp 223-224°).

11-(Di-4-morpholinylphosphinyloxy)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**10**).

To a stirred solution of **9** (1.63 g, 8.2 mmoles) in dry tetrahydrofuran (100 ml) was added a 80% dispersion of sodium hydride in white oil (0.49 g, 16.4 mmoles) and the mixture was stirred at room temperature under nitrogen atmosphere for 2 hours. Di-4-morpholinylphosphinic chloride (4.2 g, 16.4 mmoles) was then added at 0° 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 on silica gel column eluting with ethyl acetate-ethanol (9:1). First fractions were discarded and central eluates were collected and evaporated to give 2.26 g (68%) of pure (by pmr) **10** as a glassy material, which was used in the next step without further characterization; pmr: δ 3.22-3.48 (m, 8H), 3.65-3.85 (m, 8H), 4.97 (s, 2H), 6.18 (m, 1H), 6.63 (m, 1H), 6.85 (m, 1H), 7.15-7.45 ppm (m, 4H).

9*H*-Pyrrolo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**7**).

A solution of **10** (2.6 g, 6 mmoles) and formylhydrazine (0.75 g, 12 mmoles) in l-butanol (60 ml) was heated at reflux for 16 hours. The solvent was evaporated and the residue was partitioned between dichloromethane and sodium chloride solution. After drying, the organic solution was evaporated to give a residue which was purified on silica gel column eluting with ethyl acetate-ethanol (9:1). After evaporation of the solvent, the first fractions gave 0.3 g (25%) of lactam **9** and the second fractions furnished 0.9 g (65%) of **7**, mp 228-230° after recrystallization from ethanol; pmr: δ 5.05 (s, 2H, CH_2), 6.23 (m, 1H, pyrrole proton), 6.95 (m, 2H, pyrrole protons), 7.48 (m, 4H, benzene protons), 8.63 ppm (s, 1H, triazole proton).

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 69.95; H, 4.58; N, 25.35.

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