Research on Nitrogen Containing Heterocyclic Compounds. XVI. Synthesis of 1,3,4,14b-Tetrahydro-2,10-dimethyl-2*H*,10*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzotriazepine (1:1) Maleate (10-Methyl-10-azaaptazepine)

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A synthesis of the potential antidepressant 1,3,4,14b-tetrahydro-2,10-dimethyl-2*H*,10*H*-pyrazino[2,1-*d*]-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **4**, structurally related to aptazepine, is reported in four steps. The key steps of the synthesis were the formation of the tricyclic compound ethyl 10,11-dihydro-5-methyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine-11-carboxylate **6** *via* a Pictet-Spengler type condensation and the formation of the diketopiperazine **8** by cyclization of the chloroester **7** with methylamine.

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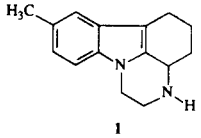
In search of new psychotropic drugs a large group of pyrazino derivatives has been synthesized.

Pharmacological investigations have shown that some of these compounds, *e.g.* pirlindole **1**, mianserin **2** and aptazepine **3**, possess properties typical of antidepressants [1].

We have previously synthesized some derivatives of 5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine system as psychotropic agents [2a,b], now we wish to report the synthesis of 1,3,4,14b-tetrahydro-2,10-dimethyl-2*H*,10*H*-pyrazino[2,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzotriazepine **4**, a compound showing great structural affinities with aptazepine.



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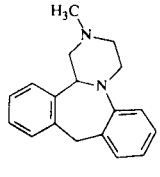

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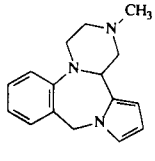

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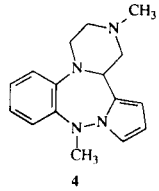

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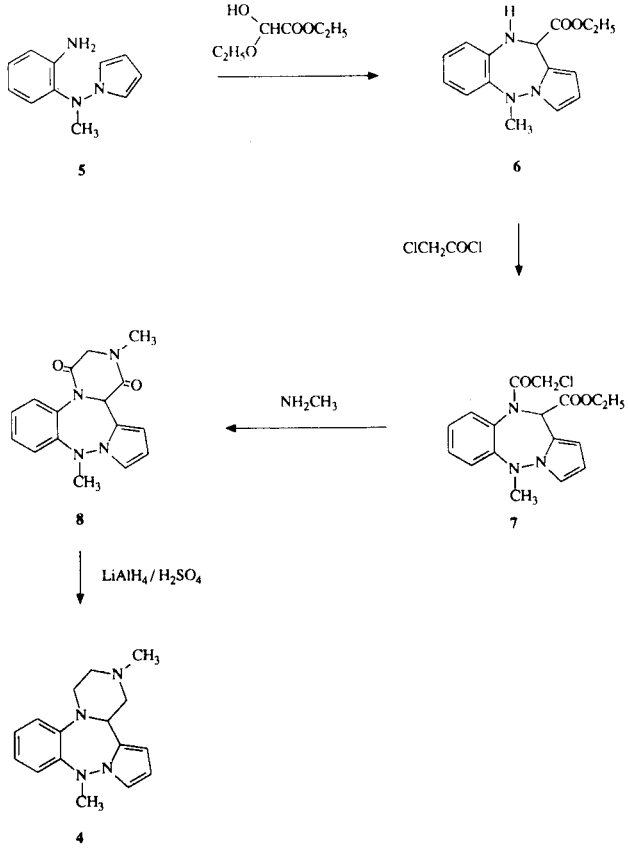
The route we choose resembles the reported synthesis of **3** [3] starting yet from the *N*-(2-aminophenyl)-*N*-methyl-1*H*-pyrrol-1-amine **5** *via* Scheme 1.

Reaction of **5** with ethyl glyoxylate ethoxy hemiacetal in ethanol afforded the aminoester **6** through a Pictet-Spengler type condensation.

Treatment of aminoester **6** with chloroacetyl chloride in methylene chloride followed by cyclization of chloroacetamido ester **7** with gaseous methylamine gave the diketopiperazine **8**.

Reduction of **8** with lithium aluminium hydride/sulfuric acid furnished the free base **4** (overall yield 53%) which on treatment with maleic acid in ethanol produced the title salt.

Scheme 1



EXPERIMENTAL

Melting points were determined on an Electrothermal IA 6304 apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 297 spectrophotometer. The pmr spectra were recorded on a Varian EM-390 spectrometer with TMS as internal standard. Merck alumina (70-230 mesh ASTM) was used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

Ethyl 5-Methyl-10,11-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine-11-carboxylate (**6**).

A solution of the ethoxy hemiacetal of ethyl glyoxylate (3.74 g, 0.025 mole) in dry ethanol (5 ml) was added dropwise to a cooled (0°) solution of *N*-(2-aminophenyl)-*N*-methyl-1*H*-pyrrol-1-amine **5** (3.74 g, 0.02 mole) in the same solvent (25 ml). The mixture was stirred at 0° for 2 hours and at room temperature overnight. After removal of the solvent under reduced pressure, the residue was subjected to chromatographic purification on alumina column, eluting with benzene. The central eluates were collected and evaporated under reduced pressure to yield 4.2 g of compound **6** (77%) as an oil which solidified on standing. An analytical sample could be obtained by recrystallizing from diethyl ether at -25°, mp 99-102°; ir (nujol): ν 3375 (NH), 1720 cm^{-1} (CO): pmr (deuteriochloroform): δ 7.13-6.53 (m, 5H, aromatic and pyrrole), 6.03 (m, 1H, pyrrole), 5.87 (m, 1H, pyrrole), 5.57 (s, broad, 1H, CH), 4.80 (s, broad, disappears on treatment with deuterium oxide, 1H, NH), 4.37 (q, 2H, methylene), 3.30 (s, 3H, methyl), 1.30 ppm (t, 3H, methyl of ethyl).

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.08; H, 6.38; N, 15.46.

Ethyl 5-Methyl-10-chloroacetyl-10,11-dihydro-5*H*-pyrrolo[1,2-*b*]-[1,2,5]benzotriazepine-11-carboxylate (**7**).

A solution of chloroacetyl chloride (2.62 g, 0.023 mole) in methylene chloride (10 ml) was added dropwise to a cooled (0°) mixture of the aminoester **6** (6.0 g, 0.022 mole) and sodium bicarbonate (2.13 g, 0.025 mole) in the same solvent (22 ml). The reaction mixture was stirred for 4 hours at room temperature, then was quenched by addition of water (20 ml) and the aqueous layer was extracted with fresh methylene chloride (2 x 25 ml). The organic layers combined were washed with sodium bicarbonate solution, then with brine and dried (sodium sulfate). After removal of the solvent under reduced pressure, the residue was subjected to chromatographic purification on alumina column eluting firstly with benzene and then with chloroform. The benzene eluates were discarded and the collected chloroform eluates were evaporated to give 6.8 g of compound **7** (88%), mp 123-126° (after recrystallization from cyclohexane); ir (nujol): ν 1740 (CO ester), 1655 cm^{-1} (CO amide); pmr (deuteriochloroform): δ 7.58-7.22 (m, 4H, aromatic), 6.95 (t, 1H, pyrrole), 6.33 (s, 1H, CH), 6.05 (m, 1H, pyrrole), 5.95 (m, 1H, pyrrole), 4.28 (q, methylene of ethyl), 4.05, 3.91 (AB q, J = 13 Hz, 2H, α-halomethylene), 3.30 (s, 3H, methyl), 1.32 ppm (t, 3H, methyl of ethyl).

Anal. Calcd. for $C_{17}H_{18}ClN_3O_3$: C, 58.70; H, 5.21; N, 12.08; Cl, 10.19. Found: C, 58.54; H, 5.26; N, 12.07; Cl, 10.37.

1,3,4,14b-Tetrahydro-2,10-dimethyl-2*H*,10*H*-pyrazino[2,1-*d*]-pyrrolo[1,2-*b*][1,2,5]benzotriazepine-1,4-dione (**8**).

A stirred solution of compound **7** (6.95 g, 0.02 mole) in ethanol (350 ml) was heated to 40° and gaseous methylamine was bubbled through for 5 hours. The reaction mixture was stirred overnight at 40°, then filtered and evaporated *in vacuo*. The residue was dissolved in chloroform and chromatographed on an alumina column by elution with the same solvent. The central eluates were collected and the solvent was evaporated under reduced pressure to yield 5.2 g (87%) of compound **8**, mp 189-190° after recrystallization from benzene/light petroleum ether; ir (nujol): ν 1670 cm^{-1} (CO); pmr (deuteriochloroform): δ 7.56-6.99 (m, 4H, aromatic), 6.86 (t, 1H, pyrrole), 5.97 (m, 2H, pyrrole), 5.52 (s, 1H, CH), 4.01 (s, 2H, methylene), 3.33 (s, 3H, methyl), 3.10 ppm (s, 3H, methyl).

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.61; H, 5.50; N, 18.97.

1,3,4,14b-Tetrahydro-2,10-dimethyl-2*H*,10*H*-pyrazino[2,1-*d*]-pyrrolo[1,2-*b*][1,2,5]triazepine (**4**) (1:1) Maleate.

Concentrated sulfuric acid (2.3 ml) was carefully dropped over 10 minutes while stirring into an ice-cooled suspension of lithium aluminium hydride (3.43 g, 0.091 mole) in dry tetrahydrofuran, then the mixture was stirred at room temperature for 30 minutes. A solution of the diketopiperazine **8** (2.13 g, 0.007 mole) in the same solvent was slowly added dropwise, then the reaction was kept at room temperature for 1 hour, cooled to -15° and quenched by slow dropwise addition of 2*N* sodium hydroxide (27.2 ml). The solid was removed by filtration and washed with tetrahydrofuran, then the combined filtrates were concentrated under reduced pressure to a residue. Dissolution of the residue with chloroform, followed by washing with water, drying with anhydrous sodium sulfate, filtration and evaporation of the solvent gave an oil which was chromatographed on an alumina column eluting with chloroform. The first eluates were collected and evaporated *in vacuo* to give 1.75 g (90%) of compound **4**; pmr (deuteriochloroform): δ 7.38-6.75 (5H, overlapped signals, m, aromatic, t (6.82), pyrrole), 5.95 (m, 2H, pyrrole), 4.38 (s, broad, 1H, CH), 3.77-3.18 (5H, overlapped signals, m, methylene, s, (3.48), methyl), 3.18-2.10 ppm (7H, overlapped signals, m, methylenes; s (2.35), methyl). A solution of compound **4** (0.8 g, 0.003 mole) in dry ethanol (3.5 ml) was added to a solution of maleic acid (0.35 g, 0.003 mole) in the same solvent (3.5 ml). The mixture was stirred for 5 minutes, then cooled to yield 0.9 g of the title salt, mp 150-153° (after recrystallization from dry ethanol mp did not change); ir (nujol): ν 1710 cm^{-1} (CO).

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.37; H, 6.49; N, 14.65.

Acknowledgement.

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