Research on Nitrogen Containing Heterocyclic Compounds. XIX: Synthesis of 8*H*-Imidazo[2,1-*c*]-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepine and its 1-Derivatives

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Reaction of 2-nitrobenzyl iodide with 1*H*-imidazole, in the presence of potassium *tert*-butoxide and 18-crown-6, gave 1-(2-nitrobenzyl)-1*H*-imidazole. Trichloroacetylation of this compound furnished trichloroacetylimidazole **8**, which on treatment with sodium ethoxide was transformed into the corresponding ethoxycarbonyl derivative **9**. Catalytic reduction of the nitro group to the amino group yielded **10**, which was then cyclized to 10,11-dihydro-11-oxo-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **11**. Treatment of this lactam with di-4-morpholinylphosphinic chloride followed by reaction of the intermediate **12** with formylhydrazine gave the title compound or its 1-derivatives when acetylhydrazine or isonicotinoylhydrazine were used instead of formylhydrazine.

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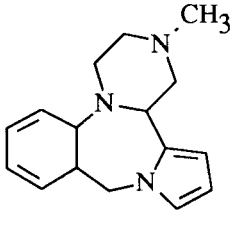
Development of new antidepressant drugs has given excellent results with the discovery of tetracyclic aptazepine **1** [1] and, more recently, with the synthesis of pharmacologically active tricyclic triazoloquinoxalines CP-68,247 **2** and CP-66,713 **3** [2].



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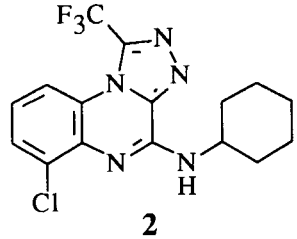

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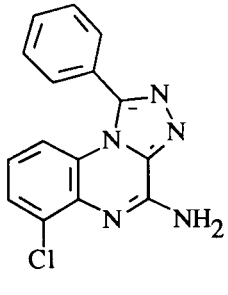

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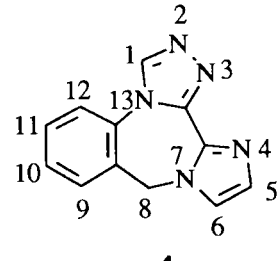
These results encourage the synthesis of new tetracyclic systems structurally related to derivatives **1-3**. Accordingly, this paper describes the synthesis of a novel tetracyclic system, 8*H*-imidazo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine **4**. Preparation of 1-methyl **5** and 1-(4-pyridinyl) **6** derivatives of **4** is also reported.



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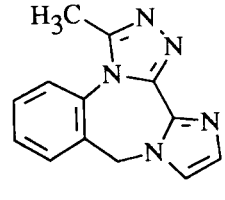

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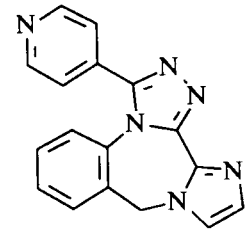

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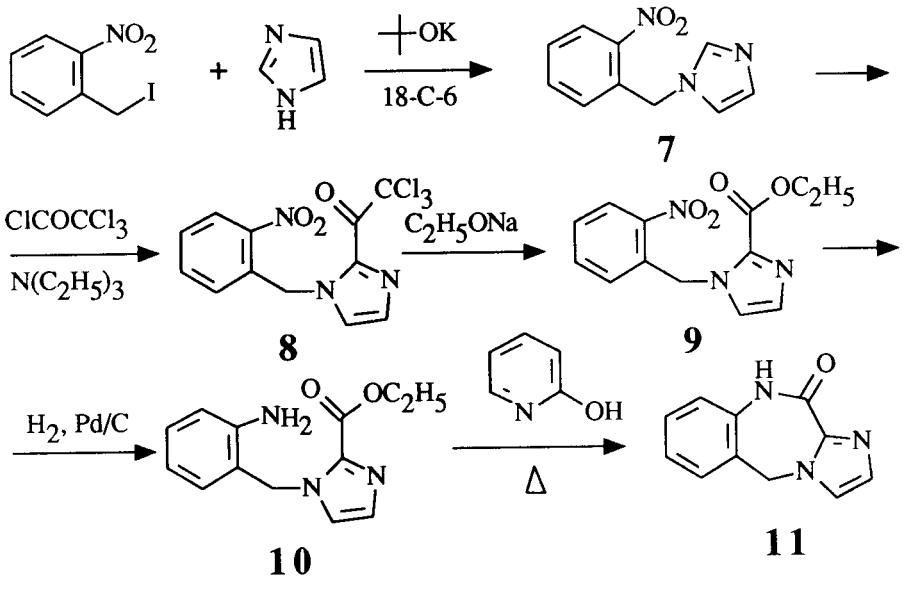
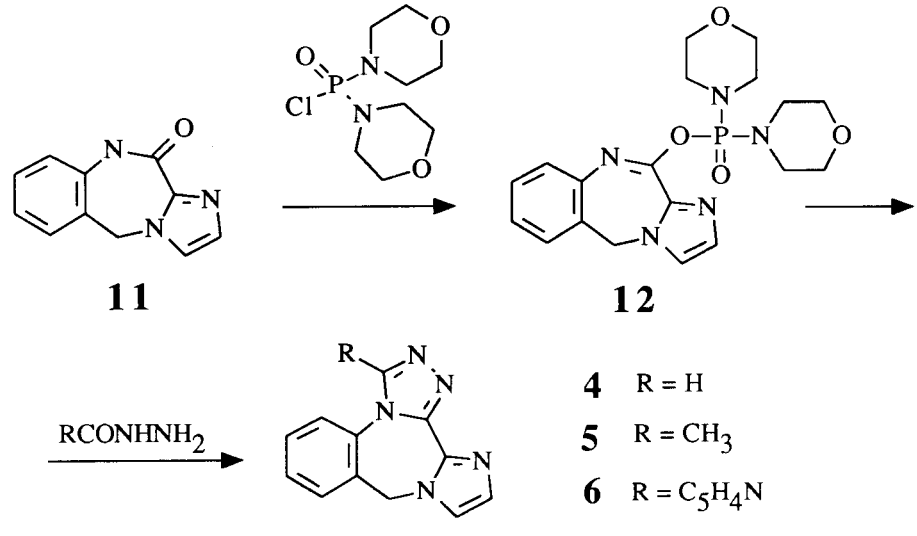
The synthesis of **4** started from 1-(2-nitrobenzyl)-1*H*-imidazole **7** [3,4], which we obtained by reacting 2-nitrobenzyl iodide with 1*H*-imidazole in the presence of potassium *tert*-butoxide and 18-crown-6 following a procedure proposed by Guida and Mathre for phase-transfer alkylation of heterocycles [5]. Compound **7** was then transformed

Scheme 1



Scheme 2



into 1-(2-nitrobenzyl)-2-ethoxycarbonyl-1*H*-imidazole **9** by treatment with trichloroacetyl chloride in the presence of triethylamine and subsequent reaction of the intermediate 1-(2-nitrobenzyl)-2-trichloroacetyl-1*H*-imidazole **8** with sodium ethoxide. Trichloroacetylation at the C-2 of 1*H*-imidazole was performed according to the method of Regel and Büchel [6].

Preparation of **9** starting from 2-nitrobenzyl chloride and 2-ethoxycarbonyl-1*H*-imidazole has been reported in a patent [7], but no data on reaction conditions and chemical and physical properties of the ester **9** were available.

Reduction of nitroester **9** with hydrogen in the presence of palladium on charcoal as the catalyst afforded the amino derivative **10**, which was converted to the lactam **11** by heating in the presence of 2-hydroxypyridine as a bifunctional catalyst (Scheme 1).

Lactam **11** was the key intermediate for the synthesis of the title tetracyclic ring. In fact, interaction of **11** with di-4-morpholinylphosphinic chloride [8] in the presence of sodium hydride afforded compound **12**, which on treatment with formylhydrazine furnished 8*H*-imidazo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine **4**. When **12** was reacted

with acetylhydrazine or isonicotinoylhydrazine under the same conditions used for reaction with formylhydrazine the tetracyclic derivatives **5** and **6**, respectively, were obtained (Scheme 2).

EXPERIMENTAL

Melting points were determined on an Electrothermal IA6304 apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 1310 spectrophotometer in nujol mulls. The ^{1}H-nmr spectra were recorded with a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as internal standard. Column chromatographies were performed on silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh). Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator) were used for tlc. Developed plates were visualized by uv light. Organic solutions were dried over anhydrous sodium sulfate. 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.

1-(2-Nitrobenzyl)-1*H*-imidazole (**7**).

To a well stirred mixture of 18-crown-6 (1.98 g, 0.0075 mole) and potassium *tert*-butoxide (8.41 g, 0.075 mole) in dry tetrahydrofuran (140 ml) a solution of 1*H*-imidazole (5.10 g, 0.075 mole) in the same solvent (140 ml) was added dropwise. After 15 minutes the resulting suspension was cooled in an ice bath while a solution of 2-nitrobenzyl iodide (19.72 g, 0.075 mole) [9] in dry tetrahydrofuran (140 ml) was added dropwise. Stirring was maintained for 16 hours at room temperature, then the mixture was concentrated to a small volume. Water and dichloromethane were added and the organic layer was separated, washed with brine and dried. Removal of the solvent furnished a crude residue, which was purified by column chromatography on silica gel eluting with ethyl acetate. Evaporation of the central eluates gave **7** (16.10 g, 85%), mp 83-85° (from benzene/petroleum ether) [10].

1-(2-Nitrobenzyl)-2-trichloroacetyl-1*H*-imidazole (**8**).

A solution of trichloroacetyl chloride (10.00 g, 0.055 mole) in dry acetonitrile (18 ml) was dropped onto an ice-cooled solution of **7** (11.17 g, 0.055 mole) in the same solvent (110 ml). After 15 minutes at room temperature a solution of triethylamine (5.56 g, 0.055 mole) in dry acetonitrile (18 ml) was added dropwise and stirring was continued at room temperature for 16 hours. The insoluble salt was removed by filtration and the solvent was evaporated to afford a crude product, which was purified by chromatography on silica gel column eluting with chloroform. Evaporation of the appropriate eluates afforded **8** (15.1 g, 79%), mp 113-115° (from cyclohexane); ir: ν 1680 cm^{-1} (C=O); pmr (deuteriochloroform): δ 6.05 (s, 2H, CH_2), 6.61-6.78 (m, 1H, benzene), 7.31-7.70 (m, 4H, imidazole and benzene), 8.18-8.35 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{12}H_8Cl_3N_3O_3$: C, 41.34; H, 2.31; N, 12.05; Cl, 30.51. Found: C, 41.50; H, 2.39; N, 12.32; Cl, 30.28.

1-(2-Nitrobenzyl)-2-ethoxycarbonyl-1*H*-imidazole (**9**).

To a solution of sodium ethoxide (prepared from 0.20 g, 0.0083 g-atom of sodium metal) in absolute ethanol (60 ml) **8** (15.00 g, 0.043 mole) was added with stirring by small portions over a period of 3-4 minutes. Stirring was maintained for 1 hour, then the solvent was evaporated. The residue was treated with crushed ice, 3*N* hydrochloric acid (3.5 ml) and extracted with ethyl acetate. The organic layer was separated, washed with brine and dried. After removal of the solvent the crude ester was purified by chromatography on alumina column eluting with chloroform. The first eluates after evaporation gave **9** (9.40 g, 80%), mp 112-114° (from benzene/cyclohexane); ir: ν 1700 cm^{-1} (C=O); pmr (deuteriochloroform): δ 1.31 (t, 3H, $COOCH_2CH_3$), 4.31 (q, 2H, $COOCH_2CH_3$), 6.01 (s, 2H, CH_2), 6.63-6.80 (m, 1H, benzene), 7.18-7.71 (m, 4H, imidazole and benzene), 8.13-8.28 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.95; H, 4.77; N, 15.26.

1-(2-Aminobenzyl)-2-ethoxycarbonyl-1*H*-imidazole (**10**).

A mixture of **9** (1.00 g, 0.0036 mole) and 10% palladium on charcoal (100 mg) in ethyl acetate/ethanol 9:1 (100 ml) was hydrogenated in a Parr apparatus at room temperature under 35 psi of pressure for 1 hour. Removal of the catalyst by filtration and evaporation of the solvent gave pure **10** (0.85 g, 97%), mp 109-111° (from benzene/cyclohexane); ir: ν 3450, 3340 (NH_2), 1690 cm^{-1} (C=O); pmr (deuteriochloroform): δ 1.40 (t, 3H, $COOCH_2CH_3$), 3.98 (broad, 2H, NH_2, disappeared on treatment with deuterium oxide), 4.41 (q, 2H, $COOCH_2CH_3$), 5.48 (s, 2H, CH_2), 6.61-7.30 ppm (m, 6H, imidazole and benzene).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.48; H, 6.20; N, 17.29.

10,11-Dihydro-11-oxo-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**11**).

A well-stirred mixture of **10** (5.00 g, 0.020 mole) and 2-hydroxypyridine (1.93 g, 0.020 mole) was heated at 170° while stirring for 48 hours under a nitrogen atmosphere. After cooling, the crude product was purified by chromatography on alumina column eluting with ethyl acetate/ethanol 9:1. Evaporation of the central eluates afforded **11** (2.00 g, 50%), mp 220-223° (from ethanol); ir: ν 3500 (NH), 1640 cm^{-1} (C=O); pmr (DMSO-d_6): δ 5.28 (s, 2H, CH_2), 7.11-7.56 (m, 6H, imidazole and benzene), 10.61 ppm (s broad, 1H, NH).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.15; H, 4.50; N, 21.12.

11-(Di-4-morpholinylphosphinyloxy)-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**12**).

A dispersion of 80% sodium hydride in white oil (0.54 g, 0.018 mole) was added to a stirred solution of lactam **11** (1.80 g, 0.009 mole) in dry tetrahydrofuran (250 ml) and stirring was maintained at room temperature under nitrogen atmosphere for 2 hours. Di-4-morpholinylphosphinic chloride (4.56 g, 0.018 mole) was then added at 0° and stirring was continued at room temperature overnight under nitrogen stream. Insoluble salt was removed by filtration and the solvent was evaporated to give a residue which was purified by chromatography on silica gel column eluting with ethyl acetate/ethanol 9:1. First fractions were discarded, then central eluates were collected and evaporated to yield **12** (3.00 g, 80%), as an oil which solidified on standing, mp 183-185° (from toluene/ligroin); ir: ν 1250 cm^{-1} (P=O); pmr (deuteriochloroform): δ 3.26-3.55 (m, 8H, morpholine), 3.68-3.88 (m, 8H, morpholine), 5.03 (s, 2H, CH_2), 7.06-7.50 ppm (m, 6H, imid-

azole and benzene).

Anal. Calcd. for $C_{19}H_{24}N_5O_4P$: C, 54.67; H, 5.79; N, 16.78; P, 7.42. Found: C, 54.73; H, 5.81; N, 16.56; P, 7.44.

8*H*-Imidazo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**4**).

A solution of phosphinyloxyimine **12** (1.00 g, 0.0024 mole) and formylhydrazine (0.29 g, 0.0048 mole) in *n*-butanol (20 ml) was refluxed for 16 hours. The solvent was evaporated and the residue partitioned between dichloromethane and brine. The organic layer was separated and dried. Removal of the solvent gave crude product which was purified by chromatography on silica gel column eluting with ethyl acetate/ethanol 9:1. Evaporation of appropriate eluates gave **4** (0.53 g, 93%), mp 251-253° (from 2-hydroxypropane); pmr (DMSO-d_6): δ 5.40 (s, 2H, CH_2), 7.20 (s, 1H, imidazole), 7.50-7.90 (m, 5H, imidazole and benzene), 9.41 ppm (s, 1H, triazole).

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.38. Found: C, 64.56; H, 4.31; N, 31.59.

1-Methyl-8*H*-imidazo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**5**).

Prepared as reported for derivative **4** starting from **12** and acetylhydrazine, **5** (0.44 g, 77%) melted at 271-273° (from ethyl acetate/ethanol); pmr (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 5.19 and 5.44 (2d, AB system, J = 15.2 Hz, 2H, CH_2), 7.11 (s, 1H, imidazole), 7.45-7.85 ppm (m, 5H, imidazole and benzene).

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.80; H, 4.67; N, 29.52. Found: C, 66.02; H, 4.73; N, 29.48.

1-(4-Pyridinyl)-8*H*-imidazo[2,1-*c*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**6**).

Prepared as reported for derivative **4** starting from **12** and isonicotinoylhydrazine. Crude product was recrystallized from 2-hydroxypropane to give **6** (0.57 g, 79%), mp 350-353°; pmr (DMSO-d_6): δ 5.55 (s, 2H, CH_2), 6.95-7.86 (m, 8H, imidazole, benzene and pyridine), 8.71-8.81 (m, 2H, pyridine).

Anal. Calcd. for $C_{17}H_{12}N_6$: C, 67.98; H, 4.02; N, 27.98. Found: C, 68.10; H, 4.13; N, 27.77.

Acknowledgments.

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[10] Lit [3] mp 82-83°; lit [4] mp 83-85°.