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A simple and efficient synthesis of 8-methyl-3,8-diazabicyclo[3.2.1]octane (azatropane) and 3-substituted azatropanes therefrom using pyroglutamic acid

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Abstract—8-Methyl-3,8-diazabicyclo[3.2.1]octane (3-azatropane) is synthesized efficiently from pyroglutamic acid making use of amide activation. The key step of the synthesis involves reduction and cyclization of a nitroenamine intermediate. Several 3-substituted analogues of this azatropane were also synthesized via this methodology and evaluated for their affinity at D_2 and 5-HT_{2A} receptors.

In continuation of our systematic studies on the synthetic utility of activated lactams derived from α-amino acids,[1] we report a simple and efficient method for the synthesis of 8-methyl-3,8-diazabicyclo[3.2.1]octane **I** (R = H, Fig. 1) and 3-substituted derivatives therefrom starting from commercially available pyroglutamic acid. 8-Methyl-3,8-diazabicyclo[3.2.1]octane, which is a bridged homopiperazine, is a common pharmacophore in a number of biologically active compounds acting on the CNS and CVS and as anthelmintics.[2–5] A noticeable feature of compounds of formula **I** is that they possess a 3-azatropane skeleton and therefore might display promising pharmacological properties. Tropane alkaloids have been important targets in organic synthesis because of their biological properties as well as to find out their mode of action.[6] Among them, cocaine and its isomers are interesting tropane alkaloids and a number of their analogues have been synthesized.[7] There are only a few reports in the literature for the synthesis of 3-azatropane.[8]

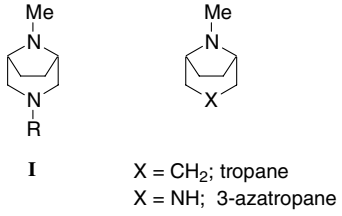

Figure 1.

8-Methyl-3,8-diazabicyclo[3.2.1]octane was synthesized in six steps as shown in Scheme 1.

Commercially available pyroglutamic acid **1** was converted to methyl 1-methyl-5-oxopyrrolidine-2-carboxylate **2** in one step following the procedure described in the literature.[9] Lactam **2** was then treated with Lawesson's reagent in anhydrous THF to give the corresponding thiolactam **3** in 78% yield. Thiolactam **3** was

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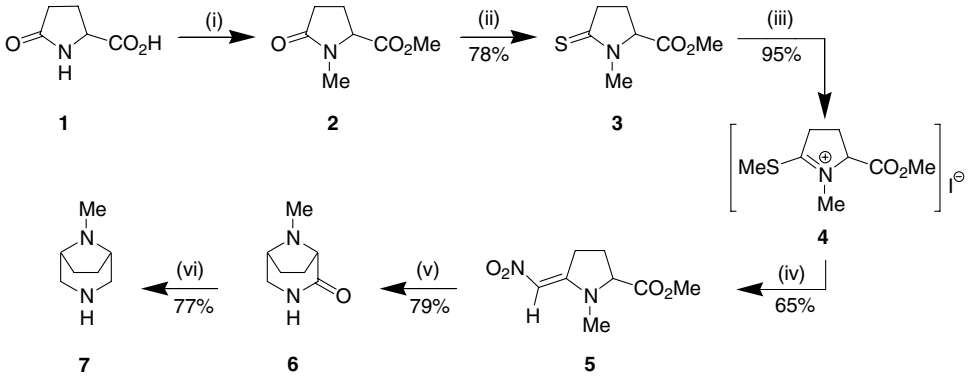


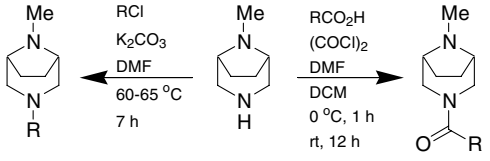
Scheme 1. Reagents and conditions: (i) Ref. 9; (ii) Lawesson's reagent, THF, rt, 3–4 h; (iii) CH_3I, PhH, rt, 12 h; (iv) CH_3NO_2, Et_3N, DMF, $N_2\uparrow$, rt, 24 h; (v) HCO_2NH_4, 10% Pd–C, MeOH, reflux, 2–4 h; (vi) LAH pellets, THF, reflux, 4–6 h.

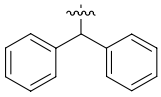
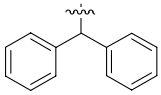
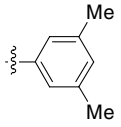
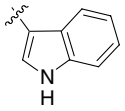
converted to methylthioimonium iodide **4** with excess CH_3I, which on further condensation with CH_3NO_2 in the presence of Et_3N yielded the corresponding nitroenamine **5** in 65% yield (Scheme 1).[10] Nitroenamine **5** was found to be thermodynamically stable as the *E*-isomer, as shown by NMR studies. Catalytic transfer hydrogenation of nitroenamine **5** over 10% Pd–C in the presence of HCO_2NH_4 in absolute MeOH at reflux, resulted in the reduction of both the double bond and the nitro group followed by in situ cyclization to give 8-methyl-3,8-diazabicyclo[3.2.1]octan-2-one (**6**)[10] in 79% yield. Finally, bicyclic lactam **6** was reduced to the desired 8-methyl-3,8-diazabicyclo[3.2.1]octane (**7**) in 77% yield by refluxing with LAH pellets in anhydrous THF (Scheme 1).[11] This amine **7** was further converted to its dihydrochloride salt by treatment with ethereal–HCl and characterized by comparison of spectroscopic (^{1}H NMR, MS) and analytical data.[12]

Derivatives **8**–**11**[13] of 8-methyl-3,8-diazabicyclo[3.2.1]-octane **7** were also prepared as described in Table 1 to establish the validity of our synthetic route and to evaluate their affinity towards D_2, 5-HT_{2A} and muscarinic receptors.

Affinities for D_2, 5-HT_{2A} and cholinergic-muscarinic receptors were determined using [^{3}H]-spiperone, [^{3}H]-ketanserin and [^{3}H]-quinuclidinyl benzilate, respectively, as radioligands. The synaptic membrane preparation used in all receptor binding experiments was prepared

Table 1. Synthesis of 3-substituted 8-methyl-3,8-diazabicyclo[3.2.1]octanes (**8**–**11**)



Compounds	R	Yield[a] (%)	Receptor binding affinity[b]		
			D_2	5-HT_{2A}	Cholinergic-muscarinic
8		49	48	53	81
9		72	43	36	80
10		38	28	30	71
11		63	23	40	41

[a] Yields of analytically pure products.
[b] % Inhibition.

according to the method described by Agarwal et al.[14] The known derivatives **8** and **9** have shown the previously reported[5,15] anti-muscarinic activity. Interestingly, these compounds have also shown 5-HT_{2A} and anti-dopaminergic activity, which was previously not described. In particular, compound **8** appears to be a new and promising 5-HT_{2A} lead. Since all of these compounds showed rather significant binding to the majority of the neurotransmitters with altogether different therapeutic potential, these structures infer the existence of certain common chemical space available within these neurotransmitters, which participate in binding. This chemical space can probably be effectively exploited to identify leads for one or more of these neurotransmitters.

In conclusion, a simple and efficient method for the synthesis of 8-methyl-3,8-diazabicyclo[3.2.1]octane (**7**) has been accomplished. Several 3-substituted analogues of 8-methyl-3,8-diazabicyclo[3.2.1]octane have also been synthesized. In addition to the previously reported anti-muscarinic activity, these compounds have also shown 5-HT_{2A} and anti-dopaminergic activity.

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10. Compounds **3**–**6** were prepared according to the methodology[1] developed by us using methyl 1-methyl-5-oxopyrrolidine-2-carboxylate **2** as a starting material.
11. *Preparation of 8-Methyl-3,8-diazabicyclo[3.2.1]octane* **7**. To a suspension of LAH pellets (5.1 g, 0.134 mol) in anhydrous THF (10 mL), a solution of bicyclic amide **6** (5.0 g, 0.036 mol) in anhydrous THF (15 mL) was added dropwise under stirring and refluxing. After the addition was complete, the resulting reaction mixture was refluxed for 24 h. After completion of the reaction, the mixture was cooled to room temperature and chilled in an ice bath and carefully transferred to a pre-chilled conical flask containing EtOAc (100 mL) and stirred at 0 °C for 30 min. To the above suspension was added EtOAc (100 mL) and water (10 mL) portion-wise, and stirring continued until the suspension turned white. The reaction mixture was filtered through Celite, which was washed with THF (3 × 20 mL) and MeOH (3 × 20 mL). The combined organic layer was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel (100–200 mesh) using $CHCl_3$–MeOH–Et_3N (94:5:1) as the eluent to afford **7** as a yellow oil (3.5 g, 77%).
12. Analytical data for compounds **3**, **5**–**7**. Compound **3**: thick yellow oil (78%); ν_{max} (CH_2Cl_2) 1744 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.39–2.47 (m, 2H), 2.78–2.79 (m, 1H), 2.88 (s, 3H), 3.72 (s, 3H), 3.81–3.83 (br s, 1H), 4.11 (m, 1H); *m*/*z* 174 [M+1]. Anal. Calcd for $C_7H_{11}NO_2S$ (173.23): C, 48.53; H, 6.40; N, 8.09. Found: C, 48.77; H, 6.68; N, 8.13. Compound **5**: yellow solid (65%), mp 111–113 °C; ν_{max} (CH_2Cl_2) 1733, 1573, 1540, 1478, 1358 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.14–2.22 (m, 1H), 2.34–2.42 (qnt, 1H, $J = 9.6$ Hz), 2.88 (s, 3H), 3.28–3.38 (q, 1H, $J = 9.6$ Hz), 3.55–3.69 (q, 1H, $J = 6.0$ Hz), 3.78 (s, 3H), 4.26–4.30 (dd, 1H, $J = 3.3$, 6.1 Hz), 6.70 (s, 1H); *m*/*z* 201 [M+1]. Anal. Calcd for $C_8H_{12}N_2O_4$ (200.19): C, 48.00; H, 6.04; N, 13.99. Found: C, 47.88; H, 6.11; N, 14.24. Compound **6**: off white solid (79%); mp 95–96 °C (lit.[16] mp 96–97 °C); ν_{max} (KBr) 1665 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.74–1.79 (t, 1H, $J = 9.6$ Hz), 2.03–2.09 (t, 1H, $J = 9.9$ Hz), 2.17–2.29 (m, 2H), 2.52 (s, 3H), 2.98–3.02 (m, 1H), 3.36–3.41 (t, 2H, $J = 5.2$ Hz), 3.66–3.71 (dd, 1H, $J = 3.6$, 5.3 Hz), 6.01 (br s, 1H); *m*/*z* 141 [M+1]. Anal. Calcd for $C_7H_{12}N_2O$ (140.18): C, 59.98; H, 8.63; N, 19.98. Found: C, 59.67; H, 8.60; N, 20.05. Compound **7**: thick oil (77%); δ_H (300 MHz, $CDCl_3$) 1.75–1.77 (br s, 2H), 2.01–2.05 (q, 2H, $J = 6.0$ Hz), 2.31 (s, 3H), 2.61–2.66 (dd, 2H, $J = 10.0$, 3.0 Hz), 3.09–3.13 (d, 4H, $J = 9.6$ Hz), 4.57 (br s, 1H); *m*/*z* 127 [M+1]. An analytical sample was obtained as a dihydrochloride salt, which was prepared by dissolving 80 mg of **7** in a 1.4 mL solution of 1 M HCl–Et_2O, mp 308–310 °C (lit.[8a] 314–315 °C). Anal. Calcd for $C_7H_{14}N_2{\cdot}2HCl$ (199.12): C, 42.22; H, 8.10; N, 14.07. Found: C, 42.56; H, 8.21; N, 13.92.
13. Compounds **8**–**11** were prepared according to the procedure described in the literature.[5,15] Compound **8**: white solid (49%); mp 113–115 °C; ν_{max} (KBr) 2900, 2800, 1493 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.08–2.18 (m, 5H), 2.48 (s, 3H), 2.52 (br s, 1H), 2.68–2.73 (dd, 2H, $J = 9.3$, 2.1 Hz), 3.36 (br s, 2H), 4.37 (s, 1H), 7.21–7.49 (m, 10H); *m*/*z* 293 [M+1]. Anal. Calcd for $C_{20}H_{24}N_2$ (292.42): C, 82.15; H, 8.27; N, 9.58. Found: C, 82.06; H, 8.26; N, 9.71. Compound **9**: off white solid (72%); mp 129–131 °C; ν_{max} (CH_2Cl_2) 1633, 1432 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.82 (br s, 2H), 2.05 (br s, 3H), 2.69 (s, 3H), 3.07–3.11 (t, 1H, $J = 6.8$ Hz), 3.59 (s, 1H), 3.77–3.84 (br s, 1H), 4.38–4.60

(dd, 2H, $J = 14.4$, 3.5 Hz), 5.50 (s, 1H), 7.11–7.36 (m, 10H); *m/z* 321 [M+1]. Anal. Calcd for $C_{21}H_{24}N_2O$ (320.43): C, 78.71; H, 7.55; N, 8.74. Found: C, 78.82; H, 7.76; N, 8.97. Compound **10**: thick oil (38%); ν_{max} (CH_2Cl_2) 1629 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.02 (m, 4H), 2.34 (br s, 9H), 3.06–3.11 (br s, 2H), 3.28 (br s, 1H), 3.38 (br s, 1H), 3.41–3.44 (m, 2H), 6.97–7.03 (m, 3H); *m/z* 259 [M+1]. Anal. Calcd for $C_{16}H_{22}N_2O{\cdot}HCl$ (294.82): C, 65.18; H, 7.86; N, 9.50. Found: C, 65.37; H, 7.60; N, 9.33. Compound **11**: white solid (63%); mp 110–111 °C; ν_{max} (CH_2Cl_2) 3452, 1636 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.72 (br s, 2H), 1.96 (br s, 2H), 2.37 (s, 3H), 2.91–3.21 (m, 2H), 3.46–3.48 (d, 2H, $J = 6.3$ Hz), 3.72 (br s, 2H), 5.29 (s, 1H), 7.14–7.72 (m, 4H), 9.61 (br s, 1H); *m/z* 270 [M+1]. Anal. Calcd for $C_{16}H_{19}N_3O$ (269.34): C, 71.35; H, 7.11; N, 15.60. Found: C, 71.09; H, 7.10; N, 15.69.

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