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SYNTHESIS OF (+)-PILOCARPINE ANALOGS WITH A 2-OXAZOLIDONE STRUCTURE

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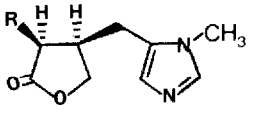
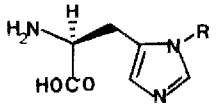
Summary: The total synthesis of three (+)-Pilocarpine analogs (**9a,9b** and **9c**) starting from L-Histidine, is described. The structure of the three new analogs contains the 2-oxazolidone structure.

(+)-Pilocarpine **1a**, an alkaloid which derives its basic properties from the imidazole ring, has received considerable attention from the point of view of synthesis because of its pharmacological significance[1]. The most recent contributions to the synthesis of this important alkaloid have pointed to the stereochemical difficulty in the cis-2,3 functionalization in the butanolide ring[2].

To substantiate the role of the butanolide ring system in (+)-Pilocarpine and in order to gain more information about the topography of the binding requirements of its cholinergic receptor, the synthesis of three (+)-Pilocarpine analogs with a 2-oxazolidone structure has been achieved[3].





1a: R= Et
1b: R= H

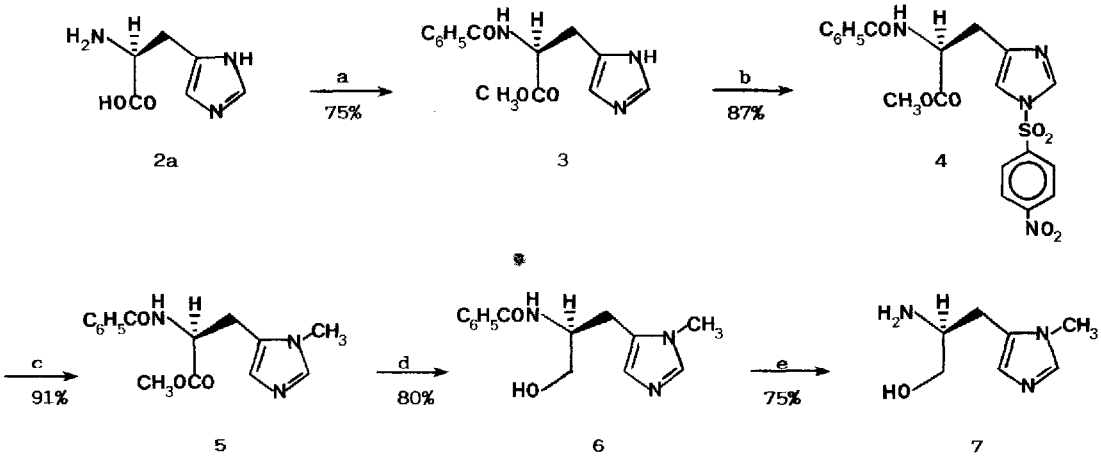
2a: R= H
2b: R= CH_3

L-Histidine **2a** was chosen as the appropiate starting material because of its structural resemblance to (+)-Pilocarpine. The preparation of N^{π}-methyl-L-histidinol **7** has been accomplished by a six-step synthetic sequence according to Scheme I[4].

The methyl ester N^{α}-benzoyl-L-histidine **3** was prepared according to the method described by Gerngross[5]. Selective N^{π}-methylation was possible thanks to a regioselective N^{τ}-protection.

Treatment of methyl ester **3** with 1.5 eq. of 4-nitrobenzenesulfonyl chloride in pyridine at -10ºC afforded a crude material from which the sulfonate **4** m.p.: 126-127ºC; $|\alpha|_D^{20}$= +10.2° (c:0.3, $CHCl_3$) was obtained upon crystallization in aqueous acetone (87%).

Proof that in this reaction the N^{π}-4-nitrobenzenesulfonyl derivate **4** was formed exclusi vely was furnished only after the N^{π}-methylation had been carried out.



a: ref.5; b: $ClSO_2Ph$-pNO_2 (1.5 eq.),pyr,-10ºC;c: 1) $(CH_3)_3O^+BF_4^-$ (1.2 eq.),CH_3NO_2, 24ºC, 15h; 2) H_2O,24ºC, 2h; d: LAH (4 eq.), THF, 24ºC, 45 min.; e: 1) 6N HCl, 80ºC, 6h; 2) KOH (EtOH).

Scheme I

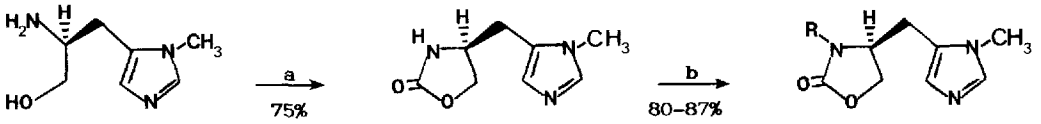
Treatment of the sulfonate **4** with trimethyloxonium fluoroborate in nitromethane followed by hydrolysis of the raw material afforded the methyl ester of N^{α}-benzoyl-N^{π}-methyl-L-histi dine **5**, m.p.:125º (95%). Conversion of **5** into N^{π}-methyl-L-histidine dihydrochloride **2b.2HCl**[6] was straightforward by treatment of **5** with 6N HCl at 80-90ºC (9h).

Reaction of **5** with LAH (4 eq.) and THF at 0ºC (45 min.) yielded a crude material from which the reduction product **6**,m.p.: 134ºC (H_2O), $|\alpha|_D^{20}$= -65º (c:0.96, CH_3OH) was isolated by crystallization in water (80%)[7].

Hydrolysis of **6** by treatment with 6N HCl at 80-90ºC led to the N^{π}-methyl-L-histidinol di hydrochloride **7.2HCl** (75%), m.p.: 176-178ºC (EtOH); $|\alpha|_D^{20}$= +1.3º (c:0.95,H_2O). Neutraliza- tion of **7.2HCl** with ethanolic KOH led to the free base **7**[8] after filtration of the KCl and evaporation of the solvent. The structural change was confirmed by the displacement of the signals corresponding to the two aromatic protons from δH_2^{im}: 8.56 ppm and δH_5^{im}: 7.30 ppm in **7.2HCl** to δH_2^{im}: 7.49 ppm and δH_5^{im}: 6.75 ppm in **7**.

Reaction of **7** with diethyl carbonate (4 eq.) in refluxing methanol (15h.) using $NaCH_3O$ as a base afforded a crude material from which it was possible to isolate the 2-oxazolidone **8**[9] (75%), m.p.: 183-185ºC (CH_3OH), $|\alpha|_D^{20}$= -10.5º (c:1.04,CH_3OH); MS (DEI): 181 (M,80) by flash chromatography on silicagel ($CHCl_3$ / CH_3OH: 7/3). Scheme II.

The new cyclization product can be considered an aza-analog of the naturally occuring alkaloid (+)-Pilosinine **1b**[1].



7 8 **9a: R= Me**
9b: R= Et
9c: R= i-Pr

a: $(EtO)_2CO$ (4 eq.), CH_3OH reflux, $NaCH_3O$ (2.2 eq.), 15h.
b: NaH (1.2 eq.), DMF, RI (1.5 eq.), 24ºC, 5-15 h.

Scheme II

Alkylation of the 2-oxazolidone 8 with methyl, ethyl and isopropyl iodides (1.5 eq.) in freshly distilled DMF at 24ºC (5-15h), using NaH (1.2 eq.) as a base, afforded **9a**, MS (CI): 196 (M+1); $|\alpha|_D^{20}$= +28.2º(c:1.1, CH_3OH); **9b**[10], MS (CI): 210 (M+1); $|\alpha|_D^{20}$=+32.5º(c:0.78; CH_3OH) and **9c**, MS (CI): 224 (M+1); $|\alpha|_D^{20}$=+85º (c:1.04,CH_3OH),m.p.:127-129ºC (CH_3OH).

The biological results will be published elsewhere.

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7. **6**: ^{1}H-NMR ($CDCl_3$): δ : 2.97 (m,2H); 3.67 (s,3H); 3.72 (d,J=5 Hz,2H); 4.19 (m,1H); 6.73 (s,1H); 7.36 (m,3H); 7.44 (s,1H); 7.70 (m,2H) ppm.
^{13}C-NMR (CD_3OD): δ : 26.30 (CH_2); 31.73 (CH_3); 52.30 (CH); 64.23 (CH_2); 127.73 (CH); 127.87 (CH); 128.13 (CH); 131.17 (CH); 134.15 (C_4^{im}); 137.50 (CH); 139.82 (C-C=O); 167.57 (C=O) ppm.

8. **7**: ^{1}H-NMR (CD_3OD): δ : 2.66 (m, 2H); 3.05 (m,1H); 3.42 (m,2H); 3.57 (s,2H); 6.75 (s,1H); 7.49 (s,1H) ppm.
^{13}C-NMR (CD_3OD): δ : 27.97 (CH_2); 31.75 (CH_3); 53.22 (CH); 65.85 (CH_2); 127.54 (CH); 130.38 (C_4^{im}); 139.41 (CH) ppm.
M.S. (CI): m/e, (%): 156 (M+1,70); 139 (10); 122 (8); 96 (50); 71 (35); 62 (100).

9. **8**: ^{1}H-NMR (CD_3OD): δ : 2.82 (d,J=6 Hz,2H); 3.58 (s,3H); 4.09 (m,2H); 4.60 (m,1H); 6.78 (s,1H); 7.52 (s,1H) ppm.
^{13}C-NMR (CD_3OD): δ : 30.22 (CH_2); 31.83 (CH_3); 52.78 (CH); 70.92 (CH_2); 127.47 (CH); 128.97 (C_4^{im}); 139.64 (CH); 161.80 (C=O) ppm.
M.S. (CI): m/e, (%): 181 (M,80); 138 (20); 96 (100); 82 (70); 68 (98).

10. **9b**: ^{1}H-NMR (CD_3OD): δ : 1.15 (t,J=7 Hz,3H); 2.80 (m,1H); 3.12 (m,1H); 3.46 (m,2H); 3.64 (s,3H); 4.00 (dd,J=4 Hz,J=8 Hz, 1H); 4.24 (m,1H); 4.38 (t,J=8 Hz,1H); 6.80 (s,1H); 7.64 (s,1H) ppm.
^{13}C-NMR (CD_3OD): δ : 12.99 (CH_3); 27.61 (CH_2); 32.48 (CH_3); 38.08 (CH_2); 54.68 (CH); 68.48 (CH_2); 126.37 (CH); 129.04 (C_4^{im}); 137.73 (CH); 160.13 (C=O) ppm.
M.S. (CI): m/e, (%): 210 (M+1,98); 166 (80); 152 (20); 123 (35); 109 (40); 97 (70); 74 (98); 60 (100).

9b.HCl: ^{1}H-NMR (CD_3OD): δ : 1.12 (t,J=7 Hz,3H); 2.93 (m,1H); 3.21 (m,1H); 3.43 (m,2H); 3.85 (s,3H); 4.03 (dd,J=4 Hz,J=8 Hz,1H); 4.34 (m,1H); 4.43 (t,J=8 Hz,1H); 7.40 (s, 1H); 8.86 (s,1H) ppm.
^{13}C-NMR (CD_3OD): δ : 13.07 (CH_3); 27.36 (CH_2); 34.64 (CH_3); 38.18 (CH_2); 54.04 (CH); 68.33 (CH_2); 118.60 (CH); 131.77 (C_4^{im}); 137.24 (CH); 159.24 (C=O) ppm.

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