PYRROLIDONIC AND PIPERIDINIC ACID DERIVATIVES

M. Baroudi, J. Robert and C. Luu-Duc*

Laboratoire de Chimie-Pharmacie, CNRS Unité de Recherche Associée 1287,
Université Joseph-Fourier, Grenoble I, F 38706 La Tronche Cedex (France)

Abstract:

Condensation of N-arylidene amines with succinyl anhydride or with glutaric anhydride giving respectively pyrrolidin-5-ones carboxylic acids 1-7 and piperidin-6-ones carboxylic acids 13-17 is described. Trans acids are obtained by fractional crystallization. Various esters 8, 11, 12, alcohols 9, 10 and imidazolides 18-30 of pyrrolidinones and piperidinones are prepared.

Introduction

Benzimidazole, pyrrolidinone and piperidone derivatives (1,2) were prepared in order to investigate new structures having a potential activity as aromatase inhibitors. Imidazole ring has been increasingly incorporated into synthesized structures due to their well-known potential biological activities like antithromboxane synthetase (3,4) and aromatase inhibitors (5-7). The pyrrolidin-5-one carboxylic acids 1-7 have been obtained by condensation of N-arylidene n-butylamines and succinic anhydride in refluxing toluene or xylene (Scheme 1). In the same way, piperidin-6-one carboxylic acids 13-17 were prepared from glutaric anhydride. The main reaction provided 2-aryl-5-one-3-carboxy-pyrrolidine or 2-aryl-6-one-3-carboxy-piperidine in satisfactory yields (Table 1). The corresponding derivatives 8, 11, 12 and 9, 10 of acidic compounds were obtained by an esterification or by a reduction reaction respectively. The appropriate acyl chloride was then refluxed with a three molar excess of imidazole in anhydrous acetonitrile under nitrogen (method A). The other reaction (method B) constituted the preferred procedure: reaction of the free carboxylic acids with *N,N'*-carbonyldiimidazole in equimolar proportions, in anhydrous THF at room temperature, gave imidazolides 18-23 and 26-30 in good yields. Finally, imidazolides 24 and 25 were obtained by a similar synthetic pathway, starting from the corresponding alcohols 9-10.

Experimental

M.p.s were determined in open capillary tubes on a Buchi micro-melting-point apparatus and are given uncorrected. IR spectra were recorded in KBr pellets for solids and between KBr discs for oils using a Perkin-Elmer 1320 spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 MHz spectrophotometer using tetramethylsilane as internal standard (chemical shifts in ppm). A DEPT sequence in ^{13}C NMR has been required for the attribution of some carbon atoms of compound 10.

Table 1: Pyrrolidinones and piperidinones derivatives (* Eb°C1 mmHg ; ** oil with decomposition in distillation)

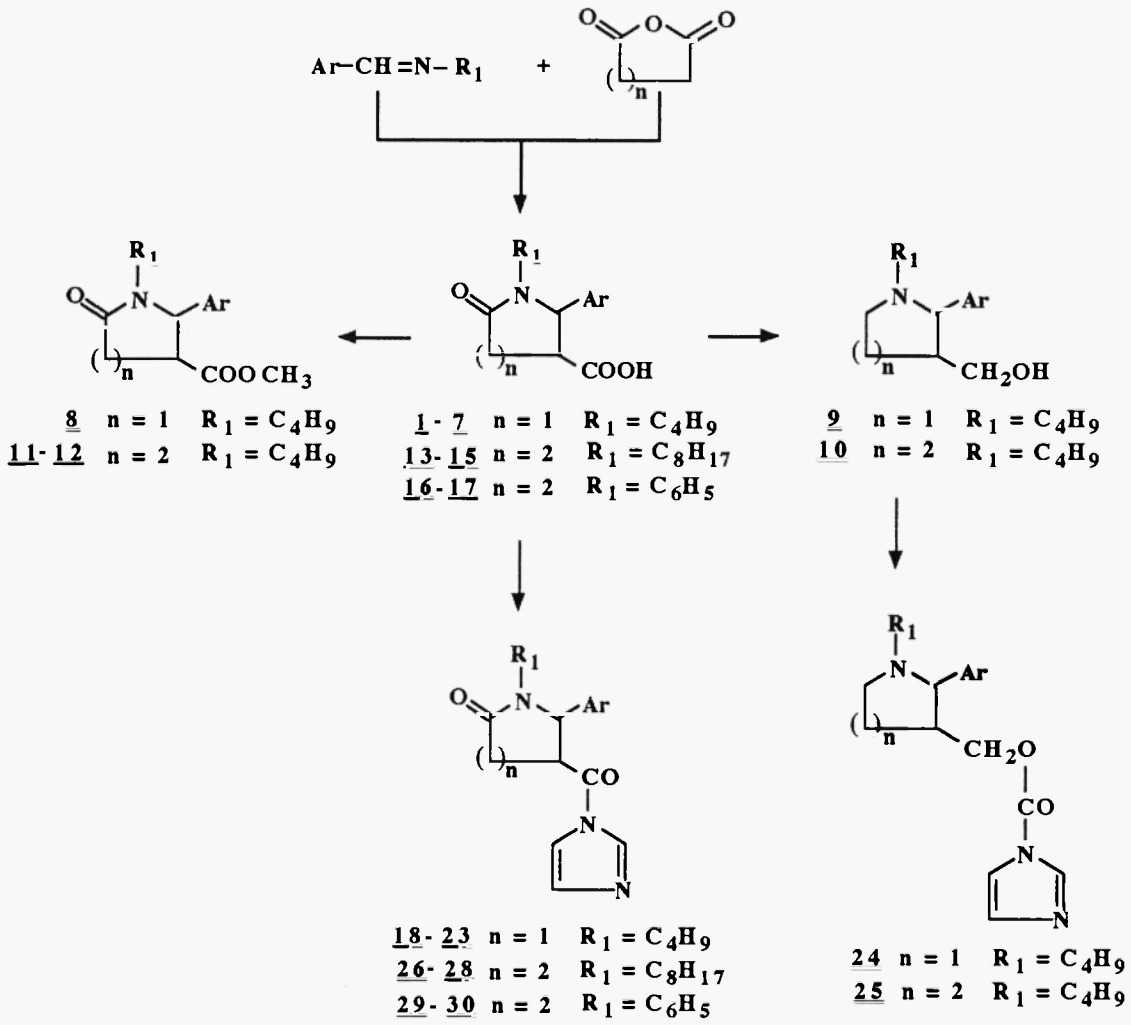
N°	Ar	R	R_1	n	Yield (%)	M.p. (°C)	^{1}H NMR (δ ppm, $CDCl_3$)
1 (8)	C_6H_5	COOH	C_4H_9	1	72	120	1.80 (m, H4'); 2.10 (m, H4); 2.40 (m, H7'); 2.60 (m, 2H5), 2.90 (m, H3); 4.00 (m, H7); 5.10 (d, H2), J_{2-3} = 2.8 Hz; 7.32 (m, 5H).
2 (8)	4-NO_2 C_6H_4	"	"	"	15	175	1.80 (m, H4'); 2.10 (m, H4); 2.40 (m, H7'); 2.60 (m, 2H5); 2.90 (m, H3); 4.00 (m, H7), 5.30 (d, H2), J_{2-3} = 2.9 Hz 7.46 (d, 2H); 8.28 (d, 2H).
3	4-Cl C_6H_4	"	"	"	60	145	1.90 (m, H4'); 2.10 (m, H4); 2.40 (m, H7'); 2.60 (m, 2H5); 2.80 (m, H3); 4.00 (m, H7), 5.10 (d, H2), J_{2-3} = 3.0 Hz; 7.21 (d, 2H); 7.40 (d, 2H).
4	4-F C_6H_4	"	"	"	60	135	1.90 (m, H4'); 2.10 (m, H4); 2.40 (m, H7'); 2.60 (m, 2H5); 2.80 (m, H3); 4.00 (m, H7), 5.10 (d, H2), J_{2-3} = 3.3 Hz; 7.11 (t, 5H); 7.25 (dd, 2H).
5	4-NH_2 C_6H_4	"	"	"	90	120	1.80 (m, H4'); 1.80 (m, H4); 2.30 (m, H7'); 2.30 (m, 2H5); 2.70 (m, H3); 3.70 (m, H7'); 4.70 (d, H2), J_{2-3} = 4.4 Hz 7.32 (m, 5H); 6.54 (d, 2H), 6.90 (d, 2H).
6	2,4-Cl_2 C_5H_3	"	"	"	37	158	1.80 (m, H4'); 2.10 (m, H4); 2.40 (m, H7'); 2.60 (m, 2H5); 2.90 (m, H3); 4.00 (m, H7'); 5.20 (d, H2), J_{2-3} = 3.3 Hz 7.15 (d, 1H); 7.37 (d, 2H); 7.60 (d, 2H)
7	4-CN-C_6H_4	"	"	"	20	117	1.60 (m, H4'); 1.90 (m, H4); 2.20 (m, H7'); 2.80 (m, 2H5); 2.80 (m, H3); 3.70 (m, H7), 5.30 (d, H2), J_{2-3} = 2.3 Hz, 7.38 (d, 2H); 7.72 (d, 2H)
8	C_6H_5	$COOCH_3$	"	"	90	130*	2.55 (m, H6b); 2.78 (m, 2H4); 3.05 (m, H3); 3.71 (s, Me ester); 4.89 (d, H2).
9	4-F C_6H_4	CH_2OH	"	"	75	oil**	0.78 (Me), 1.20 ($CH_3\underline{CH_2}$); 1.36 ($\underline{CH_2}$); 1.66 (H4a); 1.96 (H5a); 2.10 (H3, OH); 2.20 (H5a); 2.40 (H6b); 2.94 (H2); 3.30 (H4b); 3.58 ($\underline{CH_2}OH$).
10	C_6H_5	"	"	2	75	oil**	0.75 (Me), 1.15 ($CH_3\underline{CH_2}$); 1.26 ($\underline{CH_2}$); 1.29 (CH_2); 1.65 (CH_2); 1.92 (H7a); 1.76 (H3, OH), 1.92 (H7'); 2.05 (H5a); 2.06 (OH); 2.44 (H7'); 2.85 (H2); 3.11 (H6b); 3.18 ($\underline{CH_2}OH$);
11	4-F C_6H_4	$COOCH_3$	"	"	90	160*	1.92 (H4b, m); 2.01 (m, H4a) J_{2-3} = 4.0; 2.35 (m, (H7b); 2.56 (m, 2H5); 2.77 (m, H3); 3.71 (s, Me ester); 3.97 (m, H7a); 5.02 (d, H2).
12	4-Pyridinyl	"	"	"	90	155*	1.78 (m, H4b); 2.10 (m, H4a) J_{2-3} = 3.6; 2.25 (m, H7b); 2.54 (m, 2H5); 2.86 (m, H3); 3.74 (s, Me ester); 4.08 (m, H7a); 5.17 (d, H2).
13	4-Cl C_6H_4	COOH	C_8H_{17}	"	60	175	1.94 (m, H4b); 2.10 (m, H4a); 2.47 (m, H7b); 2.57 (m, 2H5); 2.82 (m, H3), J_{2-3} = 3.3 Hz; 3.91 (m, H7a); 5.09 (d, H2); 7.15 (d, 2H); 7.38 (d, 2H)
14	4-F C_6H_4	"	"	"	60	160	1.95 (m, H4b), 2.05 (m, H4a); 2.45 (m, H7b); 2.64 (m, 2H5); 2.84 (m, H3); J_{2-3} = 3.4 Hz; 3.95 (m, H7a); 5.10 (d, H2); 7.08 (t, 2H); 7.18 (dd, 2H).
15	2,4-Cl_2 C_5H_3	"	"	"	60	153	1.90 (m, H4b); 2.35 (m, H4a); 2.45 (m, H7b); 2.64 (m, 2H5); 3.00 (m, H3); 3.90 (m, H7a); 5.47 (d, H2); 7.11 (dd, H5'); 7.37 (dd, H5); 7.46 (d, H3')
16	4-Cl C_5H_4	"	C_5H_5	"	30	240	1.96 (m, H4b); 1.96 (m, H4a); 2.62 (m, 2H5); 2.96 (m, H3) J_{2-3} = 4.7 Hz; 5.34 (d, H2); 7.13 (d, 2H); 7.23 (d, 2H); 7.33 (m, 5H).
17	4-F C_5H_4	"	"	"	20	230	2.02 (m, H4b), 2.02 (m, H4a), 2.66 (m, 2H5); 2.98 (m, H3); 5.33 (d, H2); 7.08 (m, 4H); 7.24 (t, 2H), 7.36 (dd, 2H).

N°	Ar	R	R_1	n	Yield (%)	M.p (°C)	^{1}H NMR(δ ppm, $CDCl_3$)	^{13}C NMR (δ ppm, $CDCl_3$)
18	C_6H_5	CO-imidazolyl	C_4H_9	1	40	60	2.65 (m, H6b); 2.80 (m, 2H4); 2.98 (m, H3), 3.64 (m, H6a); J_{2-3} = 4.4 ; 4.99 (d, H2); 7.11 (dd, H5"); 7.30 (dd, H4") ; 7.35 (m, 5H); 8.28 (s, H2").	34.3 (C4); 40.6 (N-CH_2-R); 47.6 (C3); 65.3 (C2); 119.8 (C4' C5"); 126.6 (C2' C6'); 128.2 (C4') 128.9 (C3' C5'); 134.1 (C2"); 140.0 (C1'); 174.4 (lactam), 177.5 (amide).
19	4-NO_2 C_6H_4	"	"	"	40	oil**	2.56 (m, H6b); 2.86 (m, 2H4) 3.05 (m, H3); 3.85 (m, H6a); J_{2-3} = 4.5 ; 5.15 (d, H2); 7.12 (dd, H5") 7.31 (dd H4"); 7.37 (d, H2'H6'); 8.08 (s, H2"); 8.27 (d H3'H5').	
20	4-Cl C_6H_4	"	"	"	40	65	2.56 (m, H6b); 2.95 (m, 2H4); 3.54 (m H3); 3.70 (m, H6a); J_{2-3} = 4.4 ; 5.01 (d, H2); 7.11 (dd, H5"); 7.40 (d, 2H); 7.33 (dd, H4"); 7.45 (d, 2H); 7.95 (s H2").	
21	4-F C_6H_4	"	"	"	50	70	2.56 (m, H6b) 2.86 (m, 2H4); 2.95 (m H3); 3.60 (m, H6a); J_{2-3} = 4.4 ; 4.98 (d, H2); 7.01 (dd, H5"); 7.10 (t 2H); 7.18 (dd, 2H); 7.28 (dd, H4"); 8.15 (s, H2").	34.4 (C4); 40.6 (N CH_2 R); 47.9 (C3); 64.7 (C2); 120.0 (C4'C5"); 125.0 (C2 C6'); 128.0 (C4'), 128.3 (C3'C5'); 134.2 (C2"); 135.9 (C1'); 174.3 (lactam); 177.0 (amide).
22	2,4-Cl_2 C_6H_3	"	"	"	70	oil**	2.55 (m, H5b); 2.72 (m, 2H4); 3.05 (m, H3); 3.72 (m H5a); J_{2-3} = 3.0 ; 5.41 (d, H2); 7.05 (dd H5"); 7.10 (dd, H5); 7.16 (dd, H4'); 7.30 (dd, H5'), 7.40 (d H3'); 8.05 (s, H2").	34.4 (C4 ; 40.8 (N-CH_2-R); 46.2 (C3); 61.6 (C2); 120.2 (C4' C5" ; 127.6 (C5'); 130.2 (C3'); 134.0 (C4); 134.1 (C2"); 134.4 (C2'); 135.8 (C1'); 174.5 (lactam); 177.3 (amide).
23	4-CN-C_6H_4	"	"	"	50	oil**	2.78 (m, H6b); 2.82 (m, 2H4); 2.92 (m, H3); 3.62 (m, H6a); J_{2-3} = 4.2 ; 5.09 (d, H2) 7.11 (dd, H5"); 7.41 (d, 2H); 7.30 (dd, H4"); 7.68 (d, 2H); 8.15 (s, H2").	45.3 (C4); 47.5 (N CH_2-R) 47.6 (C3); 64.8 (C2), 112.0 (CN); 118.0 (C4'); 120.5 (C4'); 127.4 (C3'C5'); 132.8 (C2'C6'); 133.0 (C3") 134.5 (C2"), 146.0 (C1'); 174.5 (lactam); 176.8 (amide).
24	4-F C_6H_4	CH_2-O-CO-imidazolyl	"	"	78	oil**	2.64 (m H4"); 1.94 (m, H6b); 2.10 (m, H4a); 2.25 (m, H5b); 2.36 (m H6a); 2.38 (m, H3) J_{2-3} = 8.4; 2.95 (dd, H2); 3.35 (m, H5a), 4.10 (dd, H10b); 4.35 (dd, H10a); 7.00 (d, 2H); 7.28 (dd, H4"); 7.32 (d, 2H); 7.92 (s, H2").	13.0 (C9); 20.0 (C8); 26.1 (C4); 30.0 (C7); 46.2 (C3); 52.3 (C5); 53.4 (C6 ; 69.5 (CH_2-O-CO) 73.1 (C2); 115.2 (C3'C5'); 116.2 (C3" ; 129.0 (C2'C6') 136.0 (C1'), 131.4 (C4"), 138.2 (C2"); 129.0 (C2' C6'); 146.0 (CH_2-O-CO); 162.2 (C4').
25	C_6H_5	"	"	2	80	oil**	1.30 (m, 2H4); 1.76 (m, 2H5); 1.81 (m, H7b); 2.05 (m H6b); 2.07 (m, H3); J_{2-3} = 9.8; 2.32 (m, H7a), 2.88 (d, H2); 3.16 (m, H6a ; 3.91 (dd, H11b); 4.02 (d, H11a); 7.00 (dd H5"); 7.25 (m 5H); 7.28 (dd H4") 7.92 (s, H2").	13.0 (C10); 20.4 (C9); 25.3 (C5); 28.0 (C4); 28.5 (C8) 45.1 (C3); 53.0 (C6), 54.8 (C7'); 67.2 (CH_2-O-CO); 71.0 (C2); 116.2 (C5'); 127.1 (C4'); 128.0 (C2'C5'); 128.3 (C3'C5'); 131.4 (C4"); 138.2 (C2"); 142.5 (C1'); 146.0 (CH_2-O-CO).
26	4-Cl C_6H_4	CO-imidazolyl	C_8H_{17}	"	70	oil**	2.08 (m, 2H4); 2.44 (m H7b); 2.44 (m, 2H5); 3.32 (m, H3); 3.88 (m, H7a); 5.08 (d, H2); 7.08 (dd, H5"), 7.10 (d H3' H5'); 7.37 (dd, H4"); 7.40 (d H2'H6'), 8.10 (s H2"); J_{2-3} = 5.5 Hz.	29.2 (C4) 31.3 (C5); 46.0 (N-CH_2-R); 48.7 (C3); 63.0 (C2); 115.8 (C5') 129.2 (C2'C6'); 130.6 (C3'C5'); 131.5 (C4"); 135.9 (C2") 136.5 (C4'); 139.9 (C1'); 168.4 (lactam) 169.0 (amide).
27	4-F C_6H_4	"	"	"	70	oil**	2.08 (m, 2H4) 2.44 (m, H7b); 2.44 (m 2H5); 3.34 (m, H3); 3.90 (m, H7a); 5.10 (d, H2); 7.11 (dd, H5"); 7.12 (d, H3' H5') 7.25 (d, H2'H6'); 7.53 (dd, H4"); 8.10 (s, H2"); J_{2-3} = 5.8 Hz	29.9 (C4); 31.2 (C5); 46.1 (N-CH_2-R); 49.1 (C3); 63.6 (C2), 116.8 (C5"); 117.2 (C2' C6'); 129.6 (C3' C5'); 131.5 (C4"); 135.9 (C2") 137.0 (C1'); 165.0 (C4'); 168.5 (lactam); 169.0 (amide).
28	2,4-Cl_2 C_6H_3	"	"	"	65	127	2.09 (m, 2H4); 2.31 (m, H7b); 2.52 (m, 2H5); 3.51 (m H3); 4.01 (m H7a); 5.31 (d H2); 7.08 (dd, H5"); 7.11 (d H6'); 7.35 (dd, H5'); 7.39 (dd, H4"); 7.48 (d, H3'); 8.10 (s H2")	31.7 (C5); 43.6 (C4); 45.8 (N-CH_2-R); 58.1 (C3); 67.8 (C2);116.0 (C5"); 127.9 (C3') 129.3 (C2'); 130.5 (C5'); 131.5 (C4"); 132.2 (C4'); 135.2 (C1' C5'); 135.9 (C2"); 168.8 (lactam); 168.9 (amide).
29	4-Cl C_6H_4	"	C_6H_5	"	75	188	2.35 (m, 2H4); 2.80 (m 2H5); 3.50 (m, H3); 5.34 (d H2); 7.08 (dd, H5"); 7.25 (m, 9H); 7.39 (dd, H4") 8.10 (s H2"); J_{2-3} = 4.3 Hz.	22.6 (C5); 30.3 (C4); 47.6 (C3), 65.0 (C2 ; 115.9 (C5'); 127.6 (C2' C6'); 129.1 (C3' C5'), 131.6 (C4'); 131.7 (C4"); 135.9 (C2"); 137.5 (C1'); 168.6 (lactam); 169.0 (amide).
30	4-F C_6H_4	"	"	"	75	191	2.33 (m, 2H4); 2.78 (m 2H5); 3.56 (m, H3); 5.34 (d H2); 6.96 (dd, H5"); 7.28 (m, 9H); 7.39 (dd, H4") 8.10 (s H2"); J_{2-3} = 6.0 Hz.	22.7 (C5); 30.4 (C4); 47.8 (C3); 65.0 (C2); 115.8 (C2' C6') 115.9 (C5"). 128.9 (C3' C5'); 131.5 (C4"); 135.9 (C2"); 141.0 (C1'); 162.3 (C4'); 168.7 (lactam); 169.1 (amide)

General procedure for 1-n-butyl-2-aryl-5-oxo-pyrrolidine-3-carboxylic acids 1-4 and 6-7

Arylidene n-butylamines (0.135 mol) and succinic anhydride (0.15 mol) were heated in refluxing toluene or xylene under nitrogen atmosphere for 24 h. The solvent was reduced under vacuum. Analytically pure trans acid derivatives were obtained from the diastereoisomeric mixture by fractional crystallization. IR (ν_{cm-1} KBr): 2800-3100 (OH acid), 1710-1725 (CO acid), 1680 (lactam).

Compounds 13-15 and 16-17 were obtained according to the same procedure, using glutaric anhydride and N-arylidene n-octylamines or aniline respectively.



Scheme 1

1-N-butyl-2-(4'-aminophenyl)-5-oxo-pyrrolidin-3-carboxylic acid 5

Palladised charcoal (10 per cent) (0.20 g) was added to a solution of n-butyl-2-(4'-nitrophenyl)-5-oxo-pyrrolidin-3-carboxylic acid 2 (0.065 mole) in alcohol (40 ml). The mixture was allowed to react over night at room temperature under hydrogene atmosphere. Reaction was monitored by TLC using benzene/ethanol (1/1) as eluent. The theoretical volume of hydrogen was absorbed after 7-8 hours. The solid was filtered off and the filtrate evaporated on a water bath. The resulting oil solidifies on cooling to a colourless acid, m.p. 118°C. Pure pyrrolidine carboxylic acid 5 was obtained as orange needles upon recrystallization from benzene/ether (1/1), m.p. 120°C. Yield = 90%.

1-N-butyl-2-aryl-3-carboxymethylpyrrolidin-5-ones 8 and *piperidin-6-ones* 11, 12

Acid 1 (0.1 mole) was solubilized in an excess of methylic alcohol (30 ml) and solution was refluxed under gazeous hydrochloric acid atmosphere for 15 min. Heating was maintained for 30 min more and the acidic current was bubbled again in the mixture. The end of the esterification was monitored by TLC using benzene/ethanol/ammonia (8/1.5/0.5) as eluent. The solvent was evaporated in vacuum and the main product was dissolved in ether, washed with a sodium hydrogenocarbonate solution (15%) then with water. The resulting solution was dried on anhydrous sodium sulphate and distilled in vacuo. The expected ester 8 was achieved as a colorless oil. Eb_{1mmHg} = 130°C. Piperidinone derivatives 11 and 12 were obtained by the same manner starting from 1-n-butyl-2-(4'-fluorophenyl)-6-oxo-piperidin-3-carboxylic acid and 1-n-butyl-2-(4'-pyridinyl)-6-oxo-piperidin-3-carboxylic acid respectively (2).

1-N-butyl-2-(4'-fluorophenyl)-3-hydroxymethylpyrrolidine 9

A solution of 4 (0.02 mole) in anhydrous THF and ether (2 x 10 ml) was added dropwise to a suspension of $LiAlH_4$ (3.2 g) in 70 ml of anhydrous ether. The mixture was refluxed for 6 h and excess of hydride was decomposed with water (4 ml), washed with NaOH solution (4 ml, 15 %) then with 12 ml of water. The solid compound was filtered and solvents were evaporated in vacuo. The residue, in suspension in water (20 ml), was extracted with $CHCl_3$ (2 x 50 ml) and washed with a saturated NaCl solution then with water and dried. The resulting product 9 was achieved as a light yellow oil. Yield = 75 %.

1-N-butyl-2-phenyl-3-hydroxymethylpiperidine 10:

This compound was obtained by the same procedure from 1-n-butyl-2-phenyl-6-oxo-piperidine-3-carboxylic acid (2) as a colorless oil. Yield = 75 %. IR (ν_{cm-1} KBr): 3400, 3200. ^{13}C NMR with DEPT sequence (δ ppm, $CDCl_3$): 13.2 ($\underline{C}H_3CH_2$-); 20.3 ($CH_3\underline{C}H_2$-); 25.0 (C4); 27.7 (C5); 28.2 ($C_2H_5\underline{C}H_2$-); 45.9 (C3); 52.7 ($C_3H_7\underline{C}H_2$-); 54.6 (C6); 65.2 ($\underline{C}H_2OH$); 70.7 (C2); 127.1 (C4' arom); 128.2 (C2' arom); 142.5 (C1' arom).

1-N-butyl-2-aryl-3-[(1H-imidazol-1-yl)-carbonyl]-5-oxo-pyrrolidines 18-23 and 26-30

Method A: In a round bottom flask fitted with a magnetic stirrer, a condenser and a nitrogen inlet, thionyl chloride (100 ml) was added to carboxypyrrolidinones (or carboxypiperidinones) (0.03 mol) dissolved in $CHCl_3$ (100 ml). The mixture was heated for 4 h at 80°C on an oil bath, then evaporated under vacuum. The residue was treated with dry benzene and evaporated to dryness. The crude precipitate was washed with diethyl ether and allowed to react with imidazole (0.09 mol) in CH_3CN (150 ml) without

further purification. The solution was refluxed 3 h with stirring under nitrogen atmosphere. The solvent was evaporated in vacuo and imidazolides purified by crystallization.

Method B: A mixture of carboxypyrrolidinones (or carboxypyrrolidinone) (0.01 mol) and carbonyl diimidazole (0.013 mol) in anhydrous THF (30 ml) was refluxed for 3 h under nitrogen atmosphere on an oil bath. The solvent was removed in vacuo and the residue was dissolved in $CHCl_3$ (50 ml) and treated with a $NaHCO_3$ saturated solution (50 ml). Organic layers were washed with water (3 x 20 ml) and dried on anhydrous Na_2SO_4. Evaporation of the solvent and crystallization of the residue provided imidazolides having satisfactory spectral data.

1-N-butyl-2-aryl-3-[(1'H-imidazolyl)-carbonyl-oxymethyl]-pyrrolidine 24 and piperidine 25

In a round bottom flask fitted with a condenser, n-butyl-2-(4'-fluorophenyl)-3-hydroxymethyl-pyrrolidine 9 (0.01 mole) and carbonyldiimidazole (0.013 mol) in anhydrous THF (30 ml) were refluxed for 3 h under nitrogen atmosphere on an oil bath. The solvent was removed in vacuo and the residue was dissolved in $CHCl_3$ (40 ml), washed with water (2 x 20 ml) then with a NaCl saturated solution (50 ml) and dried on Na_2SO_4. Evaporation of the solvent and crystallization of the residue provided the imidazolide 24 as a yellow liquid which was purified by silica column chromatography and eluted with toluene/acetone (3/1). The pure compound was a light yellow oil. Yield = 78%. The piperidinyl imidazolide 25 was obtained by the same synthetic pathway as an colorless oil with a yield of 80%.

References

(1) F. Hida, J. Robert, C.Luu-Duc, Farmaco 49, 489 (1994)
(2) M. Baroudi, J. Robert, C. Luu-Duc, Heterocycl. Comm. 1, 147 (1995)
(3) K. Matsuda, S. Ushiyama, T. Ito, F. Asai, T. Oshima,T. Ikeda, A. Nakagawa, A.Terada and M. Yamazaki, Adv. Prostaglandin, Thromboxane, Leukotriene Res. 19, 674 (1989)
(4) E. M. Collington and H. Finch, Ann. Reports Med. Chem. 25, 99 (1990)
(5) C. D. Jones, M.A. Winter, K.S. Hirsch, N. Stamm, H.M. Taylor, H. Holden, J.D. Davenport, E.V. Krumkalns and R.G. Suhr, J. Med. Chem. 33, 416 (1990)
(6) M. Lang, Ch. Batzl, P. Furet, R. Bowman, A. Häusler, A.S. Bhatnagar, J. Steroid Biochem. Molec. Biol. 44, 421 (1993)
(7) R. Whomsley, E. Fernandez, P.J. Nicholls, H.J. Smith, P. Lombardi and V. Pestellini, J. Steroid Biochem. Molec. Biol. 44, 675 (1993)
(8) J. Robert, A. Boucherle, Ann. Pharm. Fr. 39, 337 (1981)

Received January 4, 1996