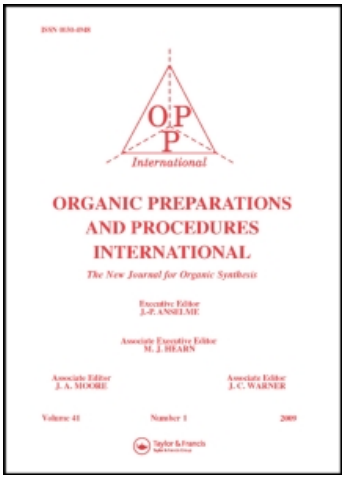

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SYNTHESIS OF N-PYRROLYL ACIDS

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SYNTHESIS OF N-PYRROLYL ACIDS

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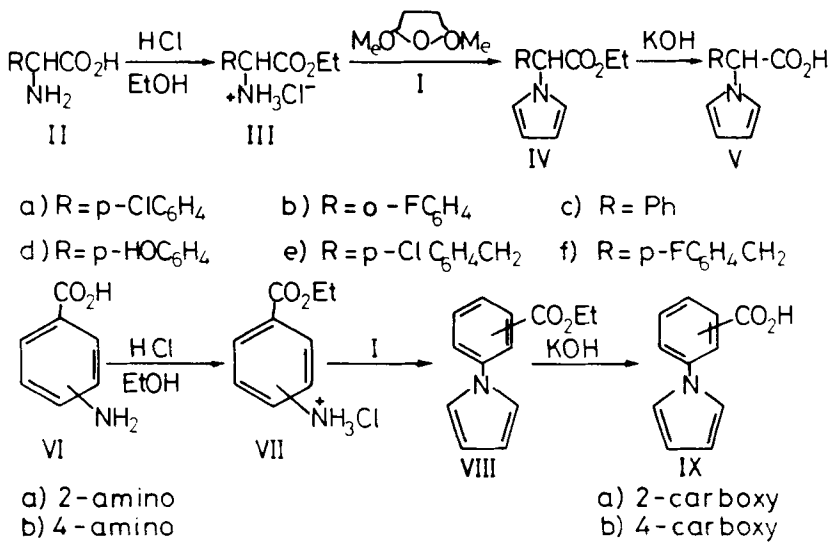
A series of N-pyrrolyl acids have been synthesized in order to study their pharmacological properties.[1] Yur'ev[2] described a method for the

transformation of furan into N-pyrrole derivatives in 3-41% yields. Elming and Clauson-Kaas[3] used the reaction of dialkoxytetrahydrofurans with primary amines in acetic acid and obtained N-pyrrole derivatives in 17-59% yields. Subsequently, Josey and Jenner[4] applied the same method using amines bearing other functional groups. In the present study, we converted amino acids into 1-(N-pyrrolyl) acids by the Clauson-Kaas method, using 2,5-dimethoxytetrahydrofuran(I).[3]



EXPERIMENTAL SECTION

Melting points were obtained with a Büchi apparatus in capillary tubes and are uncorrected. The IR spectra were recorded on a Beckman Acculab 4 Spectrophotometer using KBr disks. The UV spectra were determined on a Bausch & Lomb Spectronic 2000. The ^{1}H-NMR spectra were recorded on a Bruker 80 MHz instrument with Me_4Si as internal standard. Microanalyses were performed by Instituto de Quimica Orgánica, Juan de la Cierva, Madrid. All the acids synthesized using acetylsalicylic acid as a standard,[11] were all found to be extremely analgesic. Acids Vb and Ve were the most analgesic with protection percentages against the reference of 84% and 79% respectively, compared with 38% protection against the reference for acetylsalicylic acid. The percentage values against the reference for the other acids were between 78% (for Va) and 45% (for Vd).

Amino Acid Ethyl Ester Hydrochlorides (IIIb,d,f and VIIa,b). General Procedure A.- Dry HCl gas was passed through a suspension of 0.22 mol of the appropriate amino acid in anhydrous ethanol at a temperature 0-5°C. The reaction mixture was evaporated to dryness leaving a solid, which was then dissolved again in 100 ml of absolute ethanol. Ethyl ether (400 ml)

TABLE 1. Yields, Spectral and Physical Properties of V and IX[a]

Compound No.	Yield (%)	mp. (°C)	^{1}H-NMR(Solvent) (J=Hz)	IR(KBr) (cm^{-1})
Va[b]	87	128-130	($CDCl_3$);5.9(1H,s),6.2(2H,t,2.6), 6.5(2H,t,2.6),7.2(4H,m)	1700, 1290 1110, 740
Vb[b]	90	143-144	($CDCl_3$);4.3(1H,s),6.0(2H,t,2.6), 6.5(2H,t,2.6),7.3(4H,m)	1710, 1280 1090, 730
Vc[b]	86	95-97	($CDCl_3$);3.3(2H,c,3.4,6.8),4.8(1H, c,3.4,6.8),6.2(2H,t,2.6)6.7(2H,t, 2.6),7.2(5H,m),9.7(1H,s)	1710, 1280 1090, 730
Vd	57	150-152	(MeOH-d_4);3.3(2H,m),4.7(1H,s),6.0 (2H,t,2.6),6.6(2H,t,2.6),6.8(4H,m)	1710, 1260 1090, 720
Ve[b]	89	128-130	($CDCl_3$);3.3(1H,c,3.4,6.8),4.7(1H, c,3.4,6.8),6.1(2H,t,2.6),6.6(2H,t, 2.6),6.9(2H,d,9.1),10 (1H,s)	1690, 1270 1090, 730
Vf	89	115-117	($CDCl_3$);3.3(2H,c,3.4,6.8),4.7(1H, c,3.4,6.8),6.1(2H,t,2.6),6.6(2H,t, 2.6),6.9(2H,d,9.1),8.6(1H,s)	1720, 1280 1090, 730
IXa[b]	90	105-107	(DMSO-d_6);6.2(2H,t,2.6),6.9(2H,t, 2.6),7.2(4H,m)	1680, 1280 1070, 730
IXb[b]	88	200-202	(DMSO-d_6);6.3(2H,t,2.6),7.4(2H,t, 2.6),7.7(2H,d,10.5),8.0(2H,d,10.5)	1680, 1290 1070, 730

a) The microanalyses showed the following maximum deviations from the calculated values: C ± 0.30; N ± 0.23. b) Va, Vb,[9] Vc,[6,10] Ve,[6] IXa[7] and IXb[8] have been reported in the literature.

was added, and the mixture was left to crystallize in a refrigerator for 24 hrs. The solid obtained was collected, washed and dried giving the ethyl ester hydrochloride (Table 2).[5,6]

Table 2. Yields and Physical Properties of III and VII

Compound	Yield (%)	mp. (°C)
IIIb	86	205-207
IIId	87	185-187
IIIf	89	220-222
VIIa	86	176-178
VIIb	87	192-194

N-Pyrrolyl Esters (IVa-f and VIIIa,b). General Procedure B.- Ethyl ester hydrochloride (25 mmol) and (6.15 g) of sodium acetate were added to 0.45 mol of glacial acetic acid. The mixture was heated to boiling, until it was completely dissolved. At this point, 3.30 g of 2,5-dimetoxytetrahydrofuran was added. The mixture was kept boiling for one minute. Then the content of the flask was poured into 150 ml ice water and the mixture was stirred and extracted with ethyl acetate (80 ml). The combined ethyl acetate extracts were washed with 5% aqueous sodium carbonate and saturated aqueous sodium chloride, dried over calcium chloride and evaporated to yield a brown oil which was distilled at reduced pressure to give the N-pyrrolyl ester (Table 3).

Table 3. Yields and bp. of IV and VIII

Compound	IVa	IVb	IVc	IVd	IVe	IVf	VIIIa	VIIIb
Yield (%)	80	85	92	87	93	95	81	83
bp./torr (°C)	152/2	149/2	185/2	215/2	160/2	157/2	95/2	122/2

N-Pyrrolyl Acids (Va-f and IXa,b). General Procedure C.- Potassium hydroxide (1.4 g, 25 mmol) was added to 60 ml of ethanol:water (1:1) and the solution was added to the product previously obtained. The mixture was stirred at room temperature for 2 hrs, neutralized with 1N aqueous HCl, and ethanol was distilled off and replaced by water. The mixture was acidified to pH 1.5 with 1N aqueous HCl and extracted with chloroform. The extracts were evaporated to give a solid residue which was crystallized from ethyl ether:petroleum ether (1:1) to yield the N-pyrrolyl acid.

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