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REACTION OF ISOPROPYLIDENE MALONATE WITH CHLOROIMIDATES. A REGIO-SPECIFIC FORMATION OF CYCLIC N-ACYLATED β-ENAMINO ESTERS.

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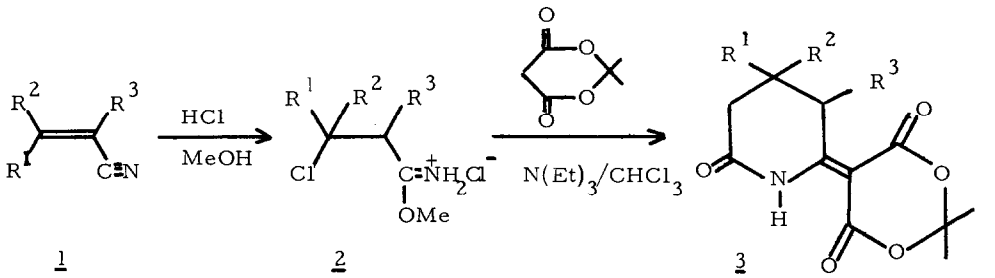
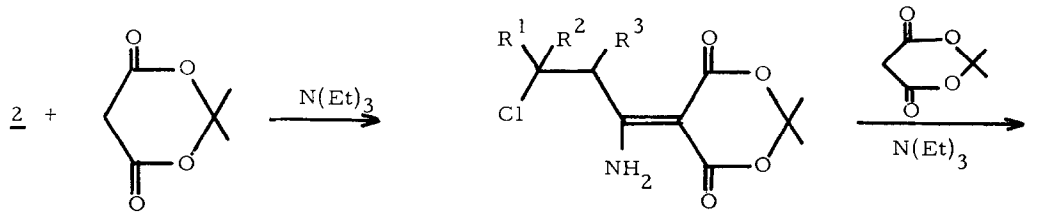
A regiospecific formation of glutarimide and succinimide derivatives is observed by reaction of Meldrum's acid with chloroimidates.

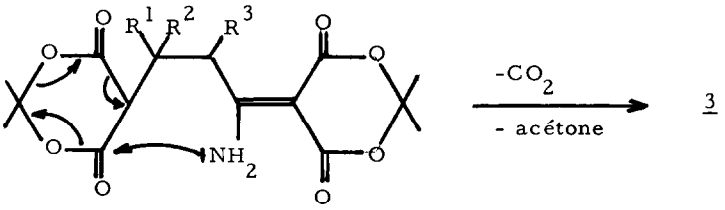
We have recently described the condensation of Meldrum's acid (isopropylidene malonate) with lactim ethers[2] or with imidates[3], leading to β-enamino diesters. The reaction of Meldrum's acid with β-chloroimidates 2 gave the imidic derivatives 3 as below :



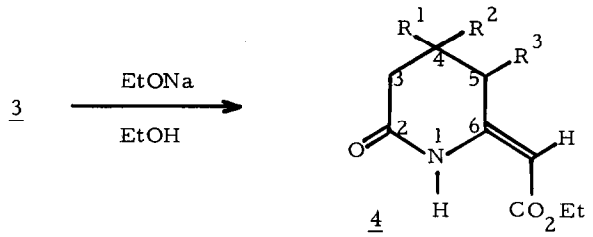
1 2 3

The imidate hydrochlorides 2 have been prepared by the classical Pinner synthesis when addition of hydrogen chloride on the C = C double bond took place[4]. The concomitant reactions with compounds 2 needed two moles of Meldrum's acid : one reacted with the imidate fonction and the second permitted the N-acylation ; a mechanism might be :





N-acyl enamino diesters 3 were opened by sodium ethoxide to give N-acyl enamino esters 4 with a Z configuration of the double bond [5].



The results were reported in the following table 1 :

Table I - Glutarimide derivatives

	R^1	R^2	R^3	2	3 (**)		4 (***)	
				Yield %	Yield %	m. p. (°C)/solvent	Yield %	m. p. (°C)/solvent
a	H	H	H	33	34	175 (EtOH)	65	82 (EtOH)
b	H	H	H	45	40	139 (EtOH)	58	17 (Et_2O, pentane)
c	CH_3	H	H	36	42	117 (EtOH)	61	49 (Et_2O, pentane)
d	CH_3	CH_3	H	23	21	116 (EtOH/Et_2O)	60	****
e	H	$-(CH_2)_4-$		28	49	132 (EtOH/Et_2O)	39	46 (Et_2O)
f	Ph	H	H	*	47	155 (EtOH)	73	119 (EtOH)
g		H	H	*	39	179	67	****

- Satisfactory microanalyses obtained for all compounds ($C \pm 0.34$, $H \pm 0.27$, $N \pm 0.27$).

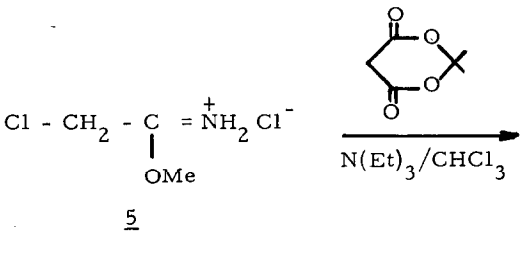
* Olefinic imidates were prepared from nitriles 1 f and g (38 % yield), the addition of hydrochloric acid did not occur on the C = C double bond[6]. However a Michael addition of Meldrum's acid were observed leading to glutarimide derivatives 3 f and g.

** ^{1}H-N.M.R. ($CDCl_3$), δ $>C(CH_3)_2$ = 1.72 to 1.78 ppm. 3f shows two singlets for the gem dimethyl radical due to the anisotropy act of the phenyl ring : δ = 1.71 and 1.76 ppm.

*** ^{1}H-N.M.R. ($CDCl_3$), δ = CH- : 4.86 to 4.96 ppm.

**** worked-up by chromatography on silica gel (Merck 60, 35-70 mesh 25 g/1g) acetone as eluant.

Meanwhile, imidate hydrochloride 5 prepared from chloroacetonitrile (80 % yield) gave the succinimide derivative 6 (43 % yield).



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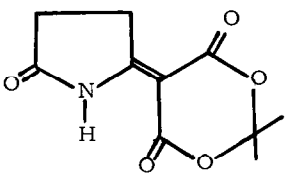


6 m. p. = 248°C ($CHCl_3$)

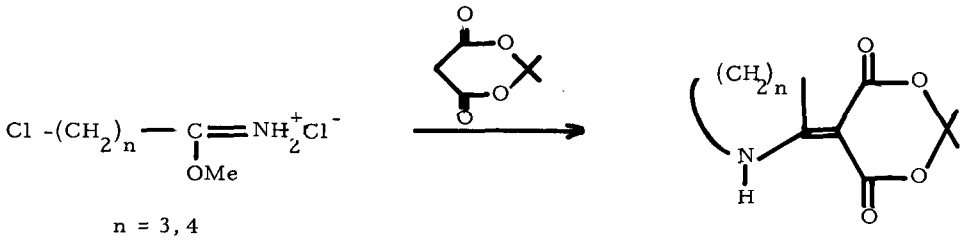
- N-acyl β-enamino diesters 3 and 6 ; general procedure

The imidate hydrochlorides 1 or 5 (0.1 mole), Meldrum's acid[7] (0.2 mole) and triethylamine (35 ml) were refluxed overnight in chloroform (200 ml). The organic layer was washed with water until pH 7-8 following by a normal work-up.

- N-acyl β-enamino esters 4 ; general procedure

The N-acyl β-enamino diesters 3 (0.1 mole) and sodium ethoxide (0.1 mole) were refluxed overnight. After evaporation of the solvent, water was added. The resulting mixture was extracted with chloroform and treated as usual.

In conclusion, imidic derivatives have been prepared when the chlorine atom is close ($n < 3$) to the imidate fonction. But, when $n \geq 3$ a ring closure takes place on the nitrogen atom[3].



n = 3, 4

By comparison with the other methods[8], this synthesis of N-acylated β-enamino esters is regiospecific and very convenient for the synthesis of naturals products like bile pigments[9].

References and Notes

1 - This work constitues a part of the thesis of P. Kapron.

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4 - The Chemistry of Amidines and Imidates, S. Patai, Ed., John Wiley and Sons, New-York, London, 1975, p. 392.

5 - Decarboxylation of 3 causes shielding of the protons H-5 ($\Delta\delta \neq 1$ ppm).

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