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STUDIES ON THE MECHANISM OF β-LACTAM FORMATION[1]

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In a previous publication[2] we presented evidence for mechanisms not involving a ketene in the formation of β-lactams from some acid chlorides, Schiff bases and triethylamine. We report here further observations which indicate that a multiplicity of factors are involved in determining the dominant mechanism of β-lactam formation by the acid chloride reaction.[3]

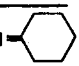
Three types of Schiff bases (I,II,III) and a variety of acid chlorides (IV,V) were used in the present study. A scrutiny of the results obtained (Table I) shows that the acid chlorides can be divided into two distinct categories: class A, possessing a nitrogen, oxygen, sulfur or chlorine at the α-position (IV) and class B with an alkyl or aryl group in that position (V). Benzalaniline (I) reacted with acid chlorides of either category to give β-lactams. The class A type of acid chlorides reacted with cyclohexone anil (II) and ethyl N-phenylformimidate(III) but the class B acid chlorides did not. The acid chlorides of class B gave only <u>trans-β-</u>lactams with benzalaniline whereas both geometric isomers were obtained from(I) and acid chlorides of class A.

The only difference between the two categories of acid chlorides appears to be the presence of an atom with a pair of free electrons at the α-position: this electron pair could play an important role in the transition states involved in β-lactam production. Böhme and coworkers[4,5] who studied the mechanism of β-lactam formation from cyanoacetyl chlorides and imines concluded that the salt(VI) is formed as an intermediate which undergoes dehydrohalogenation in presence of triethylamine to produce(VII). In the intermediate(VI) a partial positive charge should reside on the carbon atom of the imine which becomes later C-4 of the 2-azetidinone(VII). It is reasonable to expect that the atom carrying a free pair of electrons would form a loose bond with this carbon and generate a five-membered transition state (VIII). This would assure the ease of formation of a β-lactam (X) by bringing the appropriate carbon atoms C-3 and C-4 in(X) close to bond forming distance. On the basis of previous work[2] it can be expected that (VIII) could also lead to the chloro compound (IX) but this reaction would be reversible.

Our observations on the reaction between benzalaniline and a few selected acid chlorides in presence of triethylamine are summarized in Table II. In view of the fact that propionyl chloride and phenylacetyl chloride give fairly good yields of β-lactams with (I) (see Table I), the very low yield of β-lactams from β-azidopropionyl chloride, ν-azidobutyryl chloride and β-methoxypropionyl chloride is surprising. The deleterious effect of these substituents on the formation of β-lactams can be rationalized by assuming that they stabilize a transition state (for example XI) which places the potential C-3 and C-4 groups of the 2-azetidinone (XII) too far from each other for ease of bond formation. The small amounts of trans-β-lactams formed in these reactions could arise through the formation of a ketene from the acid chloride and its subsequent addition to the imine. In any case, the striking difference between the various acid chlorides in their ability to form β-lactams is one aspect of the "acid chloride reaction" that must be satisfactorily explained by any mechanism proposed for this reaction. Studies using isotope labels are in progress in our laboratory for a clearer understanding of the mechanism of β-lactam formation.[6]

Table I

β-Lactams from RCH_2COCl and Schiff Base[a]

R	Yield in per cent of β-Lactam from		
	PhN=CHPh[b]	PhN=CHOEt[c]	PhN= 
N_3	40 (c/t:3)	31	54
Phth	30 (t)	42	33
PhO	89 (c/t:6)	31	48
MeO	50 (c/t: 13)	18	14
Cl	20 (t)	traces	traces[d]
$PhCH_2S$	40 (t)	traces[d]	-
Ph	59 (t)	0	0
Me	50 (t)	0	0

(a) The acid chloride was added to a methylene chloride solution of the imine and triethylamine. No β-lactams were formed when triethylamine was added gradually to a solution of the acid chloride and the imine (II) or (III); for data on β-lactams from (I) by this method see Ref. 2.
(b) Stereochemistry determined from nmr spectra is shown in parenthesis.
(c) Only trans-β-lactams were formed as shown by nmr spectra of the crude product.
(d) Characterized spectroscopically only.

Table II .

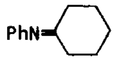
β-Lactams from XCH_2COCl and PhN=CHPh

X	Yield in percent (stereochemistry) of β-lactams	
	Method A[a]	Method B[b]
N_3	40 (c/t:3)	98 (c/t:1.3)
N_3CH_2	0	0
$N_3CH_2CH_2$	8 (t)	7 (t)
Meo	50 (c/t:3)	85 (c/t:1.7)
$MeOCH_2$	0.5 (t)	-

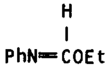
(a) The acid chloride was added to a methylene chloride solution of (I) and triethylamine.
(b) Triethylamine was added to a solution of the acid chloride and (I).

PhN=CHPh

(I)



(II)



$PhN{=}\overset{\overset{H}{|}}{C}OEt$

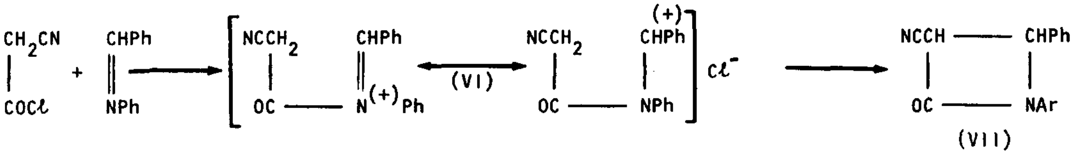
(III)

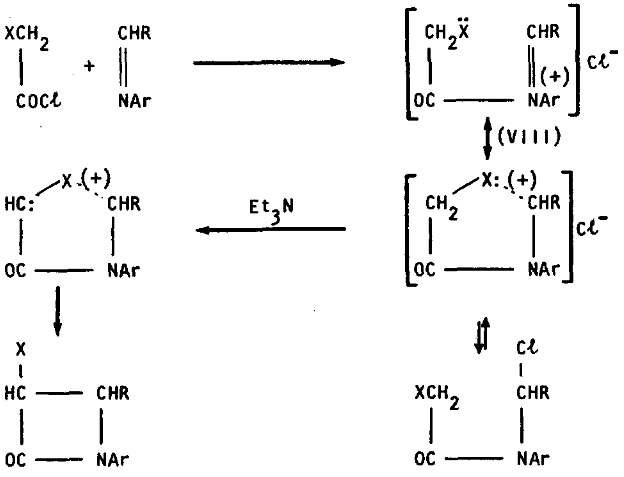
XCH_2COCl

(IV)

RCH_2COCl

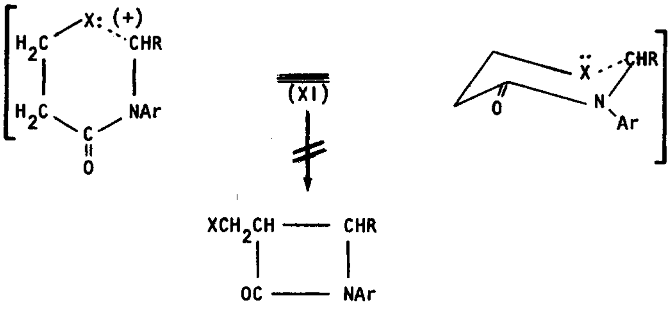
(V)





(X)

(IX)



XII

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