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STUDIES ON LACTAMS. PART XVI.[1] STEREOCHEMISTRY OF β-LACTAM FORMATION

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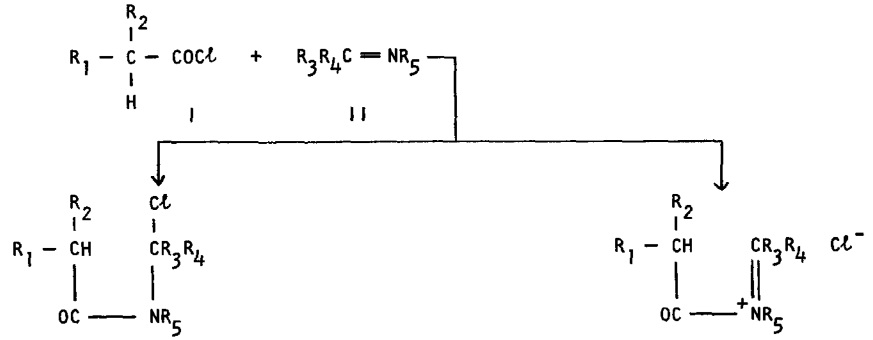
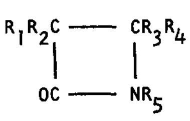
Numerous β-lactams have been prepared in recent years by the reaction of an acid chloride (I) and an imine (II) in presence of a tertiary amine. Sheehan and Ryan[2] suggested that the formation of a ketene from the acid chloride and tertiary amine and subsequent cycloaddition of the ketene to the imine was probably not the pathway to the β-lactams. One alternative to the ketene pathway involves the addition of the acid chloride to the imine to produce a reactive intermediate (III or IV) which cyclizes to a β-lactam (V) under the influence of the tertiary amine.[3,4]

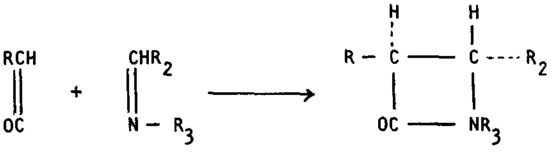


I II

III IV



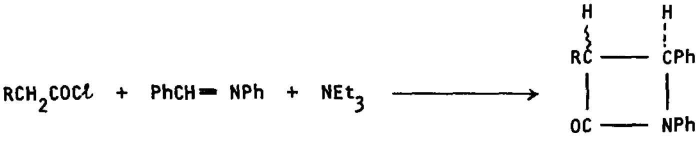
V



VI

There has been some controversy about the structure of the adduct from acetyl chloride and benzalaniline.[5] We have studied the nmr spectrum of a carbon tetrachloride solution containing equimolar quantities of acetyl chloride and benzalaniline In the nmr spectrum of the

Table 1. β-Lactams (VII) from acid chloride, benzalaniline and triethylamine



VII

R	Method[8]	β-Lactam[9]		
		mp, °C	Yield, %	Stereochemistry
Me[10]	A (B)	110-112[11]	42 (35)	trans
Me_3C	B	151-153[11]	34	trans
$H_2C{=}CH$[12]	A (B)	102-105	10 (49)	trans
Cℓ[15]	A (B)	84-90	62 (19)	trans
MeO	A (B)	141-142	55 (64)	cis
		69-73	32 (18)	trans
PhO[13]	A	192-195	38	cis
		110-113	51	trans
Ph	A (B)	131-133[11]	59 (20)	trans
p-NO_2Ph	A (B)	150-152	38 (0)	trans
p-MeOPh	B	200-204[14]	42	trans

Schiff base a one proton singlet appears at τ 1.62 which is shifted to τ 2.10 on the addition of acetyl chloride. The adduct, therefore, corresponds to the covalent structure (III); the alternative acyliminium structure (IV) would have shifted the proton signal to lower field.[6] From the spectrum it was further deduced that at 40°, 95% of the acetyl chloride had been converted to the adduct, at 65° the corresponding proportion was reduced to about 90%. Cooling to 40° returned the spectrum to its original form. Thus, there is a reversible equilibrium between the starting materials and the adduct. Similar studies with other acid chlorides and Schiff bases indicated that the reversible formation of a covalent adduct of type (III) is a general phenomenon. Such an equilibrium is likely to add to the difficulty in determining the detailed mechanism of β-lactam formation and its steric course.

Interestingly enough, the addition of triethylamine did not lead to the known β-lactam, 1,4-diphenyl-2-azetidinone, from acetyl chloride and benzalalanine. However, several other acid chlorides did react with benzalaniline to provide β-lactams whose nmr spectra indicated that sometimes both the *cis* and the *trans* isomers were formed (see Table 1). Earlier work[7] on the synthesis of β-lactams by the addition of a preformed ketene to an imine has shown that *trans*-β-lactams (VI) are formed in each case. It is evident, therefore, that "the acid chloride reaction" for β-lactam formation may entirely by-pass the ketene pathway — at least in those instances where *cis*-β-lactams are produced. Further studies are in progress on the steric course of β-lactam formation by "the acid chloride reaction".

REFERENCES

1. (a) For Part XV see, A. K. Bose, G. Spiegelman and M. S. Manhas (communicated).
   (b) Extracted from the Ph.D. thesis of G. Spiegelman, Stevens Institute of Technology, 1968.
2. J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.*, **73**, 1204 (1951).
3. H. Böhme, S. Ebel, and K. Hartke, *Chem. Ber.*, **98**, 1463 (1965).
4. H. Böhme and S. Ebel, *ibid.*, **98**, 1819 (1965).
5. (a) E. Ziegler and T. Wimmer, *Monatsh. Chem.*, **96**, 1252 (1965);
   (b) E. Ziegler and T. Wimmer, *Chem. Ber.*, **99**, 130 (1966).
6. G. A. Olah and P. Kreienbühl, *J. Am. Chem. Soc.*, **89**, 4756 (1967).
7. (a) R. Pfleger and A. Jager, *Chem. Ber.*, **90**, 2460 (1957); H. B. Kagan and J. L. Luche, *Tetrahedron Letters*, 3093 (1968).

8. Preparative method: A, 15mM each of acid chloride and benzalaniline were added to 75 ml of CH_2Cl_2 under N_2, the nmr of the solution indicated 80-95% of adduct of type III; an equivalent amount of NEt_3 in CH_2Cl_2 was added slowly and the reaction mixture allowed to stand overnight before work-up; B, same as A except acid chloride was added to a mixture of the imine and NEt_3.
9. Satisfactory spectral and analytical data were obtained for new compounds.
10. The nmr spectrum of the crude product showed signals corresponding to those reported for the dimer and trimer of methylketene: D. G. Farnum, J. R. Johnson, R. E. Hess, T. B. Marshall, B. Webster, *J. Am. Chem. Soc.*, **87**, 5191 (1965).
11. The nmr spectrum of the product was identical to that reported: H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, 941 (1964).
12. This product was obtained with *trans*-crotonyl chloride as the starting material. A similar isomerization of the acid chloride double bond has been reported, T. Ozeki and M. Kusaka, *Bull. Chem. Soc.* Japan, **40**, 1132 (1967).
13. We were unsuccessful in attempts to prepare the reportedly stable phenoxyketene; C. M. Hill, G. W. Senter, and M. E. Hill, *J. Am. Chem. Soc.*, **72**, 2286 (1950).
14. The mp reported in literature is 199°, W. Kirmse and L. Horner, *Chem. Ber.*, **89**, 2759 (1956).
15. Also see F. Duran and L. Ghosez, *Tetrahedron Letters*, 245 (1970).