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PENICILLIN IMINO CHLORIDES I. FACILE EPIMERIZATION AND KETENIMINE FORMATION IN THE PENICILLIN G SERIES.

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As part of our interest in the chemistry of penicillin imino chlorides we investigated the conversion of the imino chloride of penicillin G pivaloyloxymethyl ester 2a to its corresponding ketenimine 3a.[1] Such a transformation, promoted by triethylamine (TEA) and the like, has precedent in the work of Stevens.[2] However, in the case described herein, 2a undergoes rapid and nearly complete epimerization to 2b prior to dehydrochlorination by TEA. Thus epimeric ketenimine 3b results as the major product. We present here details of the chemistry surrounding this previously unreported process.

Penicillin G pivaloyloxymethyl ester 1a[3] was transformed to 2a by known methods[4] in 90% yield and 90% purity [ir (CH_2Cl_2) 5.62 and 5.73 μ (CO); nmr (Table I)]. The only contaminant, which resulted from partial hydrolysis of 2a during work-up, was 1a which could be clearly distinguished and accurately estimated by analysis of the nmr spectrum of crude 2a (Table I). When 2a was treated with one equivalent of TEA in $CDCl_3$ rapid equilibration ensued (< one minute) affording a mixture of 2b [nmr (Table I)] and 2a in a ratio of about 9:1 (nmr integration). During 30 minutes at room temperature 2a and 2b dehydrohalogenated slowly and gave a mixture of ketenimines 3a and 3b which was isolated as a brown oil [70%; ir (CH_2Cl_2) 4.96 (C=C=N), 5.62 and 5.73 μ (CO)]. Analysis of the mixture (Table I) revealed epimer 3b as the predominant component. Only the C-3H and gem-dimethyl signals for 3a could be clearly identified along with appropriate peaks for 1a (original 10% contaminant). However, the epimer ratio was accurately determined by

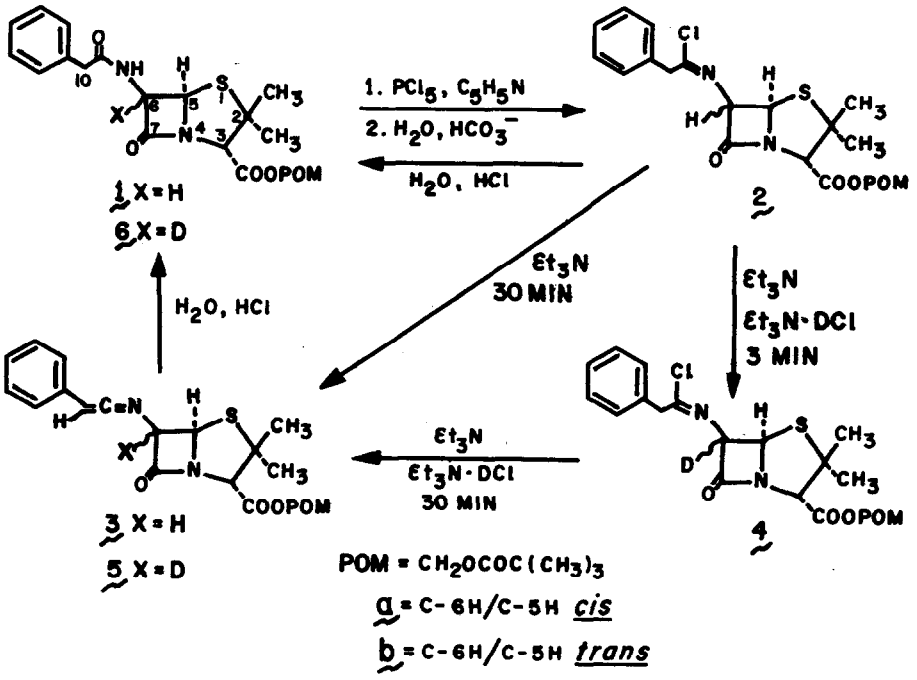

TABLE I : NMR DATA IN PPM (J IN HZ) FOR PENICILLIN DERIVATIVES

COMPOUND	SOLVENT	C-6H	C-5H	C-3H	C-10H	C-2CH_3's
1a	$CDCl_3$, D_2O, NaOD	d,5.66(4.2)	d,5.49(4.2)	S,4.40	S,3.63	S,1.45
1b	" "	d,5.03(1.9)	d,5.12(1.9)	S,4.48	S,3.56	d,1.50
2a	$CDCl_3$	d,5.33(4.0)	d,5.62(4.0)	S,4.53	S,3.99	d,1.57
2b	" "	d,5.03(1.9)	d,5.36(1.9)	S,4.56	S,3.93	d,1.56
3a	" "			S,4.42		d,1.54
3b	" "	q,4.88 (1.3 X 2.0)	d,5.09(2.0)	S,4.53	d,5.40(1.3)	d,1.52
4b	" "		S,5.36	S,4.56	S,3.93	d,1.56
5b	" "		S,5.09	S,4.53	S,5.40	d,1.62
6b	$CDCl_3$, D_2O, NaOD		S,5.12	S,4.48	S,3.56	d,1.50

hydrolyzing the ketenimine mixture with dilute acid in acetone to a mixture of 1a and 1b. Analysis of the resulting nmr spectrum (with appropriate corrections for the original 1a contaminant) revealed that 3b and 3a had been present as a 9:1 mixture. This same procedure was applied to the previous imino chloride mixture of 2a and 2b and the results corroborated our nmr analysis.

When 2a was treated with one equivalent of TEA containing a five-fold excess of TEA·DCl for three minutes, followed by rapid aqueous work-up, 4b was isolated as the major product [nmr (Table I)]. Increased reaction time (30 minutes) allowed formation of 5b which was isolated as a mixture with 5a [nmr (Table I)]. The aforementioned hydrolysis procedure was used to prepare 6b (isolated by column chromatography on silica gel with a deuterium content of about 80-90%) [ir (CH_2Cl_2) 3.01 (NH), 5.58, 5.67, 5.73 and 5.93 μ (CO); nmr (Table 1)] from either 4b or 5b, and 1b (purified as a white foam after three column chromatography treatments) [ir (CH_2Cl_2) 3.01 (NH), 5.58, 5.67, 5.73 and 5.94 μ (CO); nmr (Table I); Found: C, 59.2; H, 6.2; N, 6.5; S, 7.1] from either 2b or 3b. These experiments, in addition to interrelating the amide, iminochloride and ketenimine structures in a predictable way, provided unequivocal assignments of the C-6 and C-5 proton resonances in the nmr spectra of 2 and 3.[5]

The rate of epimerization of 2a in relation to dehydrochlorination was subject to solvent effects; when the reaction was carried out in benzene, for example, a mixture of 3b and 3a was produced in a ratio of about 3:2 (verified by hydrolysis). This isolated mixture, when redissolved in methylene chloride and treated with TEA, afforded a 9:1 mixture of 3b and 3a thus demonstrating that ketenimine 3a also epimerizes at C-6.

Others have described the epimerization of various penicillin derivatives when certain structural requirements are met.[6] The penicillins reported herein fall within the category of substances in which one would expect facile C-6 epimerization. As expected, the imino chlorides derived from esters of penicillin V, carbenicillin, oxacillin and cephalothin also epimerize.[7] Consistent with the observations of Stoodley,[6e] we have found the epimerization process to be a true equilibrium[7] and we favor an ElcB mechanism or the like to explain the results.[6d] Because of the instability of intermediates 2b and 3b (decomposition) they could not be isolated in pure form. However, the spectral techniques employed allowed their ready identification in solution. Both 2b and 3b, were used in subsequent synthetic studies, the results of which will be reported in detail elsewhere.

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1. I. Katagawa, K. Hori, H. Osada and N. Fujii, Toyama Chem. Ind. Co. Ltd., Japan Patent 7224038 (1972). This report appeared after the completion of our own work and due to major discrepancies in data we repeated their procedure for penicillin G ethyl ester (excess $COCl_2$ in THF at -18° for 4 hrs followed by evaporation to dryness in the cold). These workers reported the following data for the resulting ketenimine; ir 4.44 (CH=C=N), 5.65 μ (β-lactam CO); nmr 7.35 ppm (s, 1, CH=C=N). Our data included ir 4.44 μ and a singlet at ∿7.35 ppm in the nmr. However, based on our data for 3b we would expect the ir resonance for ketenimine to appear at about 4.96 μ and the nmr resonance for the ketenimine proton to appear as a doublet (coupled to C-6H) at about 5.40 ppm. Additionally, we failed to observe a β-lactam carbonyl stretch at ∿5.60 μ in the ir, and the nmr spectrum in general lacked the detail one would expect of an intact penicillin molecule. We feel these data discrepancies cannot be explained simply on the basis of differing ester group and/or stereochemistry at C-6. We suggest that the ir peak at 4.44 μ best correlates with an isocyanate moiety. One can envision an isocyanate forming from $COCl_2$ and an amine, the latter arising after decomposition of starting material under the conditions of the reaction. Our own experience with phosgene as a reagent for preparing penicillin ketenimines has been that a tertiary base is required as coreactant.

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7. Unpublished results of R. D Carroll. Manuscript to be submitted for publication elsewhere.