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PENICILLIN IMINO CHLORIDES III. A NOVEL TRICYCLIC β-LACTAM DERIVED FROM THE REACTION OF PHENYL-5-INDANYLOXYCARBONYLKETENE WITH THE IMINO CHLORIDE OF PENICILLIN V METHYL ESTER

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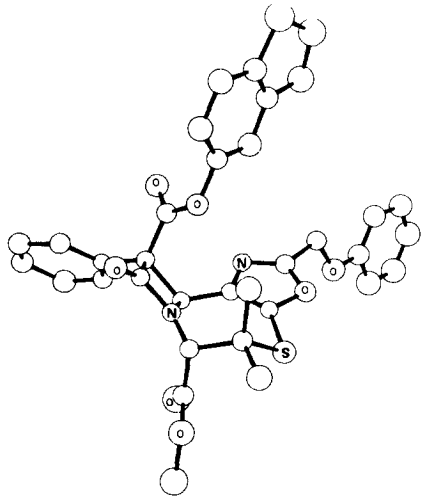
In a previous communication[1] we described base-catalyzed rearrangement of the imino chloride **1** of penicillin V methyl ester to oxazole **9**. In the work described herein we report formation of novel β-lactam **8** which arises, after a complicated series of steps, from the interaction of **1** with ketene **3**. In the reaction, **3** affords an intermediate which serves as its own internal base and initiates rearrangement to **8**. Our findings confirm the existence of imine **7** as a labile intermediate in both the previous[1] and present work and allow us to offer a mechanistic interpretation of the results.

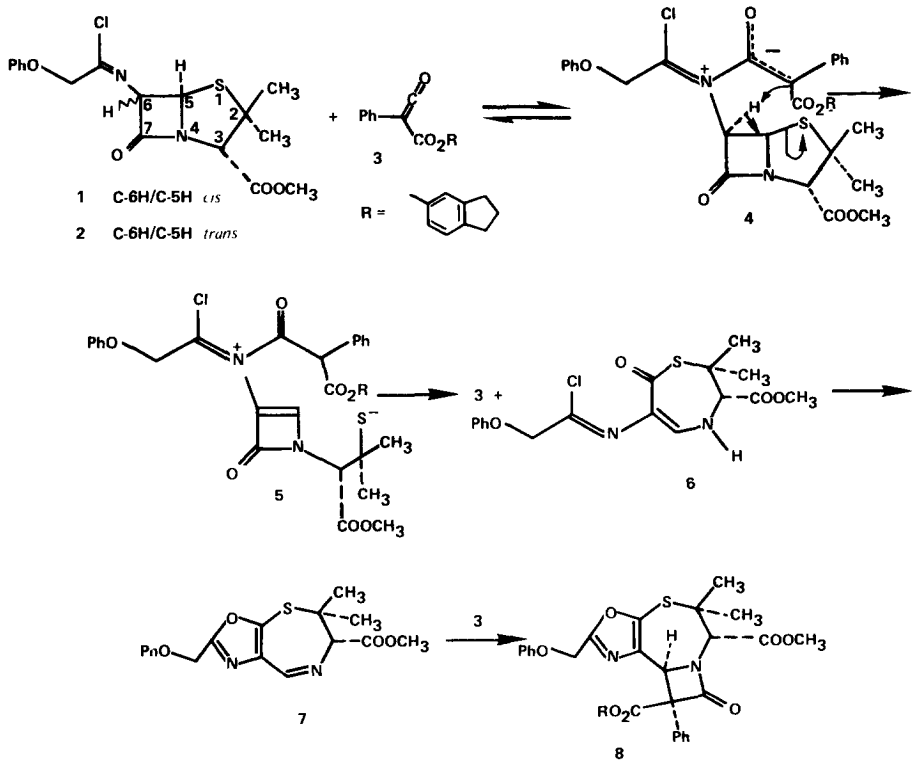
Treatment of **1** in CH_2Cl_2 with one equivalent of ketene **3** (prepared from its acid chloride with pyridine) at room temperature followed by aqueous workup, chromatography and recrystallization, afforded a 67% yield of a new substance [mp 147-8° (ethanol); ir (KBr) 5.62, 5.67 and 5.69 u (CO's); uv max (CH_3OH) 264 (10.2), 269 (10.5), 275 nm (8.2); nmr ($CDCl_3$) 6.5-7.9 (m, 13, Ar*H*), 5.67 (s, 1, lactam *H*), 5.05 (s, 2, $PhOCH_2$), 4.93 (s, 1, $CHCO_2CH_3$), 3.70 (s, 3, OCH_3), 2.76 (unsymm t, 4, J = 7.0 Hz, $CH_2CH_2CH_2$), 1.95 (unsymm quintet, 2, J = 7.0 Hz, $CH_2CH_2CH_2$), 1.73 and 1.49 ppm (s's, 6, 2 x CH_3); mass spectrum *m/e* (rel intensity) 624 (4), 491 (34), 346 (20), 278 (45), 253 (80), 145 (100); $[\alpha]_D^{24}$ + 143° (1, CH_2Cl_2); Found: C, 67.3; H, 5.2; N, 4.8; S, 5.2]. In addition the reaction mixture also afforded a 2% yield of oxazole **9**[1]

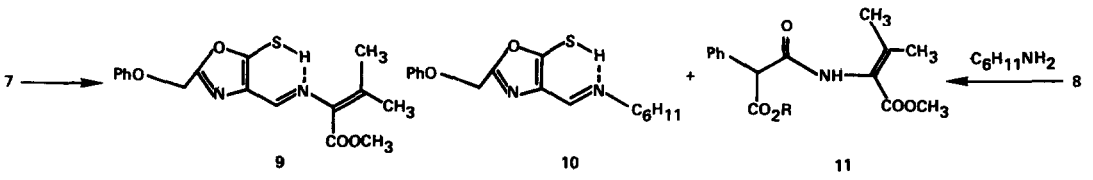
We could not rationalize the formation of **9** since we knew, based on our own and other work,[2] that penicillin imino chlorides are stable to pyridine and the like and rearrange to oxazoles only in the presence of stronger bases such as TEA.[1] Since pyridine was the only base employed in this work (present in the reaction as pyridine hydrochloride), oxazole **9** could not form by a route involving direct base catalyzed epimerization and rearrangement of imino chloride **1**.[1] This contention was amplified by reacting epimer **2**[1] with ketene **3** and isolating a good yield of the new rearrangement product. Carefully conducted nmr time studies revealed the buildup of product from either **1** or **2** and showed clearly that **1** and **2** did not interconvert during the reaction.

In search of additional structural information, we treated the rearrangement product with cyclohexylamine (CHA) and obtained oxazole **10** and amide **11** in high yield. Oxazoles **9** and **10** have been related previously[1] and amide **11** was confirmed by spectroscopic and combustion data. With the thought in mind that oxazole **9** might be a precursor to product, we reacted it with ketene **3**. No reaction took place. Unable to derive a structure totally consistent with these findings and the above data, we turned to X-ray analysis for a solution. The results, exhibited below,[3] revealed the rearrangement product to be novel tricyclic β-lactam **8**.



With structure **8** in hand we were able to rationalize all of the above results and propose the following mechanistic interpretation:



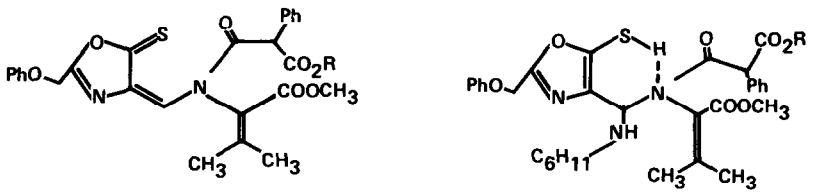


9 10 11

Imino chloride **1** reacts with ketene **3** affording intermediate **4**. The enolate moiety in **4**, *via* an intramolecular proton abstraction at C-6, affords enethiolate **5** irreversibly. The above nmr studies with **1** and **2** support the irreversible nature of this step. Species **5**, in a precedented reaction,[4] undergoes formation of thiazepine **6** with concomitant generation of ketene **3**. Ring closure of **6** affords imine **7** which, in turn, is trapped by **3** in a cycloaddition reaction affording **8**. The small amount of **9** observed arises from imine **7** in a minor competing reaction.

Some additional comments are in order supporting our view that proton transfer (**4**→**5**) involves an intramolecular reaction which proceeds by way of a 5-membered ring. One could argue that enolate **4** is first protonated by pyridine hydrochloride and then free pyridine abstracts the proton at C-6 affording **5**. However, the work of both Abe and Isaka[5] speaks against this possibility. One could also argue that **4** abstracts the proton at C-6 intermolecularly. However, **4** is a crowded molecule and we feel it unlikely that two such species should interact easily in an acid-base reaction. It is our view, in fact, that crowding in **4** accounts for the irreversible nature of the **4**→**5** transformation. Enethiolates have been previously proposed as intermediates in the epimerization of other penicillin derivatives,[4b] a point which finds no support in the present work. Although we realize that alternate mechanisms exist, we believe that the above proposal best fits the observed data.

Of some interest is the pathway by which CHA transforms **8** to oxazole **10** and amide **11**. Although we have no direct evidence bearing on this point, we suggest that CHA, in the first step, causes ring opening of **8** to give a species such as **12** which, in turn, undergoes proton transfer and addition of free CHA. The resulting intermediate **13** rearranges further affording the observed products. It is a species such as **13** which also likely accounts for the transformation of oxazole **9** to oxazole **10**.[1]



12 13

Finally, we think it is of general interest to discuss further the role of ketene **3** in the chemistry described herein. Abstraction of the proton at C-6 by the enolate portion of **4** represents, to our knowledge, the mildest method now known (in terms of base strength) for initiating such a proton abstraction and subsequent rearrangement. The concept of using ketenes such as **3** as specific base operators, attaching them to one portion of an organic molecule and using the resulting intermediate to initiate further chemistry at a remote site, may have additional applications in synthesis.[6] This concept remains of current interest to us especially as it applies to the present work and its extensions, both for penicillins and cephalosporins.

Acknowledgments:

The authors would like to thank C. Ogston and L. Smith for competent technical assistance and Professor D. S. Kemp and Dr. I. M. Goldman for helpful discussions. Crystallographic calculations were performed at the University of Arizona Computing Center.

References:

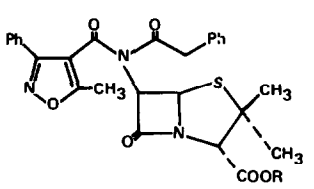
1. *R. D Carroll and L. M. Smith,* **J. Het. Chem.**, *445 (1975).*

2. *J. Abe, T. Watanabe, T. Take, K. Fujimoto, T. Fujii, K. Takemura and K. Nishiie, U.S. Patents 3,658,792 and 3,668,200 (1972).*

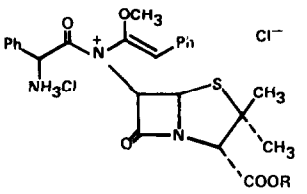
3. *Compound* **8** *crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules in a cell of dimensions:* **a** *= 12.774(5),* **b** *= 36.095(15),* **c** *= 6.970(3)Å, V = 3211.4Å^3. Diffraction data were collected on a Picker FACS-I diffractometer using CuKα radiation and a θ-2θ scan. The data were corrected for Lorentz and polarization effects. No correction for absorption was made. Of the 2804 data collected 972 were considered as unobserved ($F_o^2 < 3\sigma(F_o^2)$). The structure was solved by a combination of direct methods and Fourier techniques and refined by full-matrix least-squares to yield R_1 = 0.078, R_2 = 0.094. $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $R_2 = (\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2)^{1/2}$ where $w = 4F_o^2/\sigma^2(F_o^2)$ with the quantity minimized being $\Sigma w(F_o - F_c)^2$. The number of parameters for this problem (405) exceeded the capacity of our computer. Consequently, the molecule was partitioned into three overlapping fragments and each fragment was independently refined. Computer programs used in this study included Dewar's FAME, Main's MULTAN, Zalkin's FORDAP, Iber's NUCLS and Johnson's ORTEP. The refinement involved 1832 data having $F_o^2 \geq 3\sigma(F_o^2)$ and anisotropic thermal parameters for the 45 non-hydrogen atoms. The estimated standard deviations for bond lengths and angles, at the present stage of refinement, are in the range 0.01-0.02Å and 0.6-0.8° respectively, and the observed distances and angles are consistent with the proposed molecular formulation.*

4. *(a) B. Ramsey and R. J. Stoodley,* **Chem. Commn.**, *450 (1971); (b) S. Wolfe, W. Lee and R. Misra,* **ibid.**, *1067 (1970); (c) J. Jackson and R. Stoodley,* **ibid.**, *14 (1970); (d) O. Kovacs, B. Ekstrom and B. Sjoberg,* **Tetrahedron Lett.**, *1863 (1969); (e) A. Vlietnick, R. Roets, P. Claus and H. Vanderhaeghe,* **ibid.**, *285 (1972); (f) J. Jackson and R. Stoodley,* **J. Chem. Soc. Perkin Trans.**, *1063 (1972).*

5. *Abe and coworkers prepared diacylamine* **i** *and showed that it did not epimerize at C-6 in the presence of pyridine, but did when treated with triethylamine. See ref. 2.*



I



II

Isaka and coworkers claim and support the existence of **ii** *as an intermediate in the conversion of a penicillin G ester to an ampicillin ester. A pyridine-like base was employed in the process and no C-6 proton abstraction was observed. See I. Isaka, T. Kashiwagi, K. Nakano, N. Kawahara, A. Koda, Y. Numasaki, S. Kawahara and M. Murakami,* **J. Pharm. Soc. Japan, 92,** *454 (1972). We feel that both* **i** *and* **ii** *bear electronic and stereochemical features quite similar to those in* **4.**

6. *For a review of reactions of various types of ketenes, see H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y. (1967), chapter II and references cited therein.*