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# A NOVEL REARRANGEMENT OF A 6-FLUOROPENICILLIN DERIVATIVE

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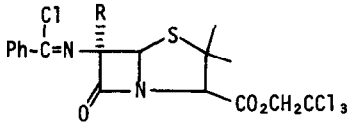
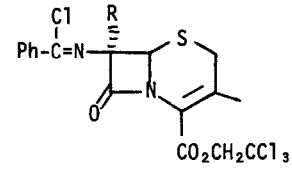
Much recent effort has been directed toward the synthesis of penicillins and cephalosporins that are substituted in the $C_6$ or $C_7$ position, respectively.[1a-m] While many derivatives have been made, we felt that it would be of particular interest to synthesize penicillins and cephalosporins with a fluoro group occupying this position. In the past, the synthesis of an appropriate Schiff base has been used effectively to activate the $C_6$ or $C_7$ position for anion formation. The anion can then be reacted with a variety of reagents to give numerous derivatives.[1c,e,f,g,h,j,k,L] In fact, in a recent report, perchloryl fluoride was used in conjunction with this method to synthesize a $C_7$ fluoro Schiff base, but unfortunately, the fluorine was lost during attempts to hydrolyze the Schiff base.[1L] We have also synthesized the $C_7$ fluoro Schiff base, and upon hydrolysis, these same results were encountered in our laboratory; however, it occurred to us that the imino chloride function might be applied in the same manner as a Schiff base to activate the $C_6$ or $C_7$ position. Imino chlorides can be hydrolyzed to amines by alcohols, but offer an additional advantage in that they are readily converted directly to amides by aqueous hydrolysis.

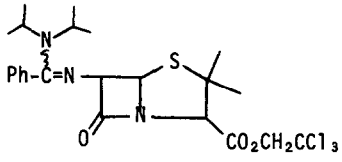
Imino chlorides 1a and 2a were readily prepared from the corresponding amides (5a and 6a), by reaction with $PCl_5$ following the procedure of Hatfield.[2] When imino chlorides 1a and 2a were reacted with lithium diisopropyl amide in DMF at -78°, the expected generation of an anion at $C_6$ or $C_7$ did not occur. Instead the diisopropyl amide reacted with the imino chloride function to form amidines 3 and 4 in good yield. Reaction of the imino chlorides with lithium diisopropyl amide in THF at -78° gave the $C_6$ or $C_7$ anions which could then be fluorinated by the addition of an equivalent of perchloryl fluoride dissolved in DMF, giving 1b and 2b in good yields. The stereochemistry of the fluoro substituent was initially presumed to be $\alpha$, based on analogy with previous alkylations and acylations of the Schiff base anion, which occurred selectively at the $\alpha$-face.[1c,d,f,k,L]



1a: R = H
b: R = F



2a: R = H
b: R = F



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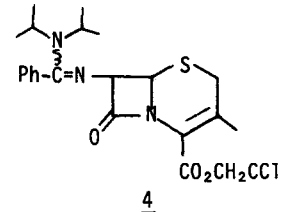

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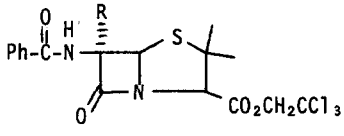
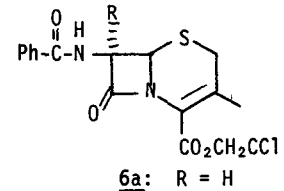
A mild and efficient method was sought for converting imino chlorides to amides. We found that when imino chlorides 1a or 2a were dissolved in 20% $H_2O$/DMF and treated with an equivalent of $AgNO_3$, reaction occurred immediately to give amides 5a and 6a in quantitative yields. Similar results were obtained with aqueous acid hydrolysis (80% acetic acid/water) carried out at 60° for 15 min.



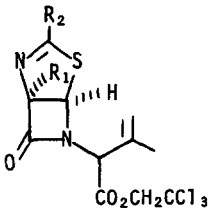
5a: R = H



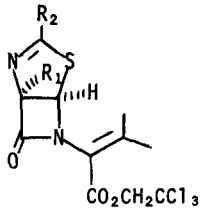
6a: R = H
b: R = OH

When either of the two hydrolysis methods was applied to the 7-fluoro imino chloride, 2b, the fluorine was lost and the hydroxy derivative, 6b, was obtained in a manner analogous with results observed with the fluorine substituted Schiff base.[1L]

In contrast, attempts to hydrolyze the penicillin fluoro imino chloride, 1b, by either the $AgNO_3$ or aqueous acid procedures resulted in formation of three new products in which the $C_6$ fluorine atom was retained. Examination of the crude product mixture by nmr indicated that the major component (~70%) was compound 7a. Efforts to purify 7a by preparative tlc resulted in its conversion to 8a, although a small amount of 8a (~9%) was also evident in the nmr spectra of the crude product mixture. The structures of compounds 7a and 8a were established by comparison of their nmr spectra with the nmr spectra of compounds 7b and 8b, which were obtained previously in these laboratories by Cooper and coworkers.[3]



7a: $R_1$ = F, $R_2$ = Ph
b: $R_1$ = H, $R_2$ = $CH_2OPh$

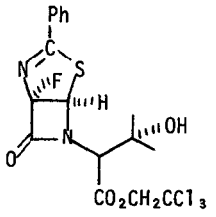


8a: $R_1$ = F, $R_2$ = Ph
b: $R_1$ = H, $R_2$ = $CH_2OPh$

In addition to 7a and 8a, a small amount of a third product, 9 (15% of crude reaction mixture), was obtained from the attempted hydrolysis reaction of the 6-fluoropenicillin imino chloride. This compound gave a correct elemental analysis for the expected 6-fluoropenicillin benzamide, however, the ir (no amide carbonyl stretching frequency) and uv data (max at 260 nm, $\varepsilon$=18,000) were not correct for the benzamide structure.

The structure of 9 was determined by x-ray diffraction analysis. The compound crystallizes from isopropanol in the acentric triclinic space group, P1, with one molecule in a unit cell having the dimensions a = 8.784 ± 0.004 Å, b = 10.577 ± 0.004 Å, c = 5.962 ± 0.004 Å, $\alpha$ = 101.99 ± 0.01°, $\beta$ = 103.90 ± 0.01° and $\gamma$ = 80.47 ± 0.01°. The density observed by flotation in zinc sulfate solution is 1.48 g $cm^{-3}$, compared to 1.49 g $cm^{-3}$ calculated for $C_{17}H_{16}Cl_3FN_2O_4S$. A total of 1767 reflections, of which 213 were "less-than" reflections, were measured on a four-circle automated diffractometer using filtered copper radiation. Since the compound is not stable to x-rays, three crystals were used for the data collection.

The structure was solved by comparing the sharpened Patterson synthesis with electron density maps phased on possible sulfur and chlorine positions. Least-squares refinement of the structure using anisotropic temperature factors for all atoms except the hydrogen atoms, which were placed at assumed positions, gave an R value of 0.094. The x-ray data are not sufficiently accurate to permit assignment of the absolute configuration; however, the three asymmetric centers probably have the same chirality as those of a normal penicillin molecule. Details of the crystal structure will be published elsewhere.



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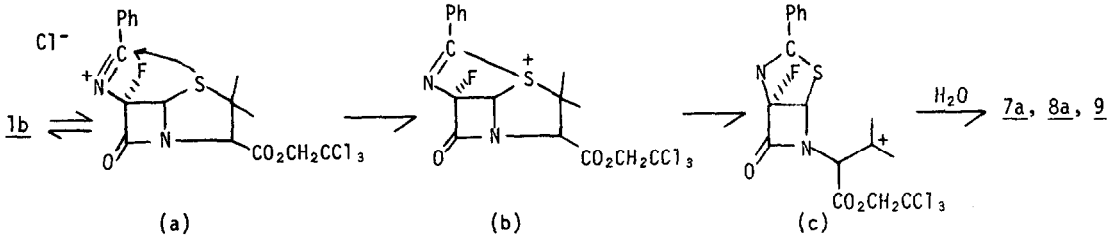
Normal aqueous hydrolysis of imino chlorides has been reported to proceed via a two-step mechanism which involves an intermediate ion pair.[4] An ion pair intermediate can also be used to explain the novel rearrangement of the penicillin imino chloride which occurs when fluorine occupies the C-6 position. The presence of the fluoro function should highly activate the nitrilium ion for nucleophilic attack. Further, the angle between the two rings of penicillin, and the cis stereochemistry of the $C_5$ sulfur and $C_6$ nitrogen aid in making the internal addition of the thiazolidine sulfur possible. The resulting sulfonium ion (b) could then proceed by ring scission to give carbonium ion (c), which would be expected to eliminate $H^+$ to give olefins 7a and 8a, and add water to give alcohol 9. Apparently, when hydrogen occupies the $C_6$ position,




the nitrilium ion is not sufficiently activated for internal sulfur attack. In the desacetoxycephalosporin system (2b), the larger angle between the two rings probably prohibits sulfur from making an approach close enough to the nitrilium ion to intercept it and thus a more unusual mode of hydrolysis is observed.

The acids derived from compounds 8a and 9 were tested and found to be substantially lacking in biological activity.

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