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A Novel Cephalosporin Dehydrothiazine Ring Cleavage Mode.

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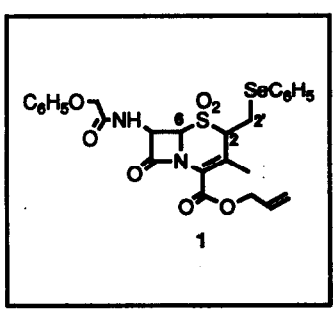
Abstract: The oxime and the tosylhydrazone of the phenoxyacetylcephalosporin-2-carboxaldehyde **4** have been shown to undergo novel and similar rearrangements in basic media. These processes resulted in the cleavage of the Δ^3 double bond, with retention of all the atoms of the starting materials.

Recent years have seen the advent of the microbiologically very important thienamycins and carbacephalosporins. This has led to keen interest in devising *intramolecular* processes, whereby the sulfur atom of thiacephalosporins is either replaced by carbon to afford carbacephems, or is lost with concomitant C(2)-C(6) bond formation to yield carbapenems. Indeed, experimental precedence for the former has been established[1] — on generation of a radical at C(2') of the cephalosporin sulfone **1**, sulfur dioxide was lost and the original C(2') carbon assumed the C(1) identity of the newly formed carbacephalosporin.

We sought other ways of doing this and viewed oximes of the structural type **5** as candidates for this type of cleavage-reclosure sequence, as shown in Scheme 1. (Examination of models indicated that orbital overlap in **5** is less favorable for formation of a five-membered ring.) It was during the investigation of this potential synthetic sequence that we uncovered an interesting and novel mode of cleavage of the cephalosporin dehydrothiazine ring.



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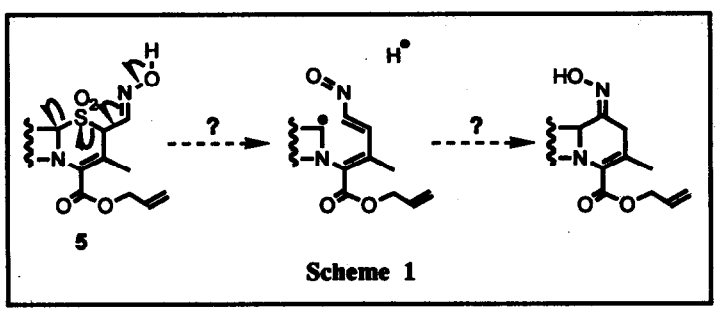
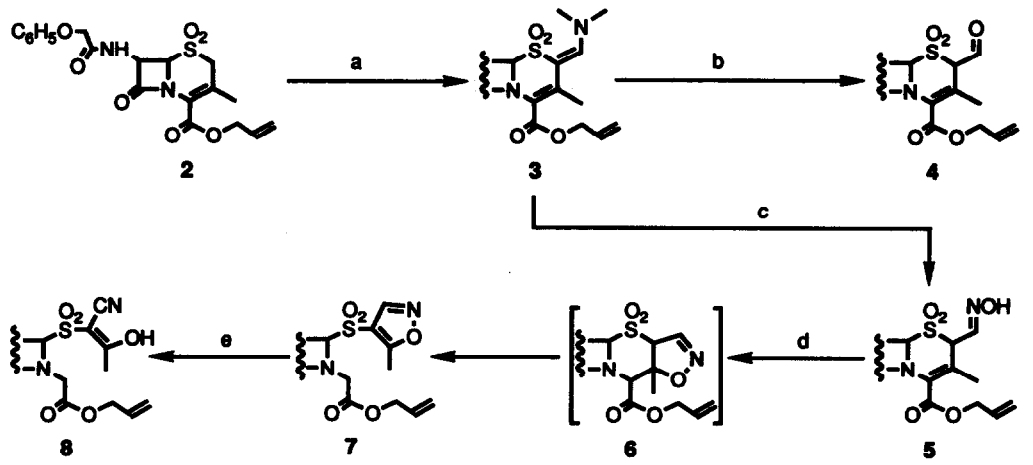


5

Scheme 1

The required cephalosporin oxime **5**[2] was prepared in a 71% overall, two-step, yield by first reacting **2** with Vilsmeier reagent and pyridine in CH_3CN to give **3**, and then treating **3** with $NH_2OH.HCl$ and CF_3CO_2H (Scheme 2), the CF_3COOH being necessary to obtain satisfactory yields. All attempts to convert aldehyde **4** to **5** gave generally poor results.

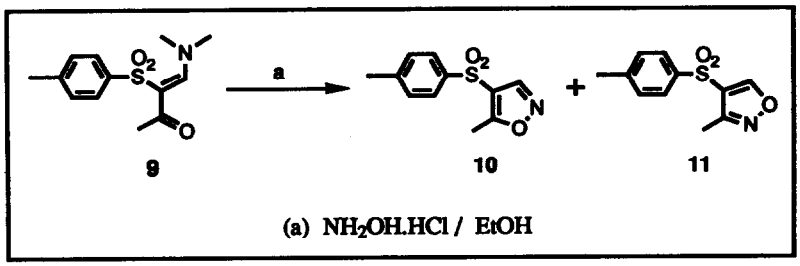


Scheme 2: (a) $(CH_3)_2N{=}CH\text{-}Cl^+.Cl^-$/ pyridine / CH_3CN; (b) $NH_2OH.HCl$ / N HCl /CH_3CN; (c) $NH_2OH.HCl$ / CF_3COOH / CH_3CN; (d) $NH_2OH.HCl$ / CH_3CN 60° or pH 10 phosphate buffer / CH_3CN 1:1, 10 min.; (e) 0.7 eq. NaOH, pH 10 phosphate buffer / CH_3CN 1:4, 2h.

NMR studies, investigating the preparation of oxime **5**, revealed that the oxime readily underwent rearrangement. This was first noted by the appearance of two new NMR signals, at 1.34 and 1.41 ppm (unassociated with **3** or **5**) upon treatment of **3** with $NH_2OH.HCl$ in CH_3CN at 60°C for 3 h. On heating for longer periods of time, the NMR spectrum of the crude products was suggestive of a three component mixture consisting of **3**, **5** and yet an additional new compound. The new compound, which became the principal product, was seemingly formed at the expense of the one(s) exhibiting the proton NMR signals in the 1.3 to 1.4 ppm region.

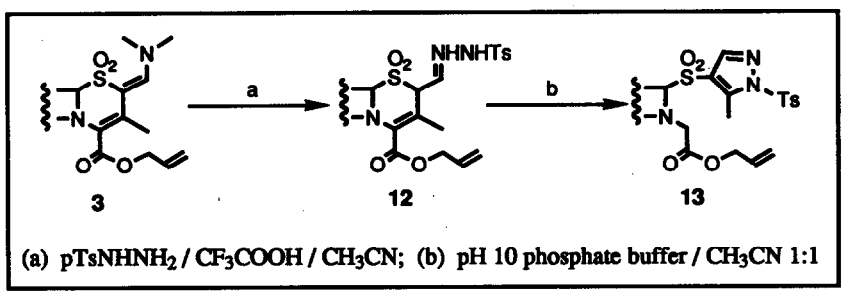
We conjectured that the oxime **5** was being converted to **7** in the manner shown in Scheme 2. Intramolecular Michael addition of the oxime oxygen of **5** to the unsaturated ester function could give the two tricyclic structures encompassed by **6** (two possible dihydroisoxazole *cis* ring junctions), with methyl groups exhibiting NMR signals at 1.34 and 1.41 ppm. Intermediate **6** could, in turn, afford the isoxazole **7** upon proton transfer.

A variety of data conformed to the structure of **7**.[3] The high resolution FAB-MS of the new compound was in accord with its elemental composition, and the high resolution FAB-MS/MS of the parent MH^+ ion produced a major fragment corresponding to scission between the sulfone group and the β-lactam ring. The IR spectrum indicated retention of the β-lactam. Comparison of the NMR spectrum of **7** with that of a mixture of **10** and **11**, obtained by refluxing **9** with $NH_2OH.HCl$ in EtOH, then chromatography, showed concordance of details.[4,5]



Further confirmation of structure **7** was derived from the fact that isoxazoles are known to undergo ring cleavage to give cyanoketones.[6] Indeed, while it was later found that a 63% yield of isoxazole **7** could be obtained by stirring **5** in 1:1 CH_3CN/ aq. pH 10 phosphate buffer for 10 minutes; **7** itself was converted in a 58% yield to **8** on being stirred in 4:1 CH_3CN/ aq. pH 10 buffer in the presence of 0.7 eq. of NaOH. The structure of **8** was supported by several pieces of information.[7] Its FAB-MS gave a protonated molecular ion of the correct mass, and peaks characteristic of nitrile and β-lactam groups were found in the IR spectrum. The absence of an NMR -$SO_2(CN)CHCO$- singlet, and a strong UV absorption indicated that the enol structure is preferred over the keto structure.

We also investigated tosylhydrazone **12** as a possible progenitor of a sequence analogous to that shown in Scheme 1. The tosylhydrazone was also found to undergo rearrangement involving a cephalosporin dehydrothioazine ring cleavage giving pyrazole **13**, as shown below. The FAB-MS and NMR of this compound conform with the cyclic structure.[8]



Summarily these are representative of a novel, relatively clean, cleavage mode of the Δ^3 double bond of a cephalosporin dehydrothiazine ring. As far as we are aware, it is the first example of this occurring by a non-oxidative intramolecular mechanism.

References and footnotes

1 Halligan, N. G.; Spry, D.O.; Blaszczak, L. C. Organic Free Radicals: Fifth International Symposium, Zurich, 18-23 September, 1988.

2 Compounds **3**, **4**, **5**, **7**, **8**, **9**, **10** and **11** (mixture), **12**, and **13** all gave correct elemental analyses.

3 **7**: IR (KBr) ν 1801 (β-lactam) cm^{-1}. FAB-MS, MH^+ = 464.1141 (calculated for $C_{20}H_{22}N_3O_8S$ is 464.1128). FAB-MS/MS of m/z 464 (MH^+) gave a mass of 317.1151 (calculated for $C_{16}H_{17}N_2O_5$ is 317.1137). ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (1H, s, isoxazole ring-H), 7.90 (1H, d, J = 10.7 Hz NH), 7.37-6.96 (5H, m, phenyl-H), 5.98 (1H, dd, J = 4.9, 8.7 Hz, β-lactam-H), 5.95-5.85 (1H, m, allyl-CH), 5.38-5.29 (3H, m, β-lactam-H and allyl=CH_2), 4.66-4.48 (5H, m), 4.02 (1H, d, J = 18.5 Hz 1/2 N-CH_2), 2.70 (3H, s, CH_3).

4 **10**: ^1H NMR (300 MHz $CDCl_3$) δ 8.34 (1H, s, isoxazole ring-H), 7.9-7.2 (4H, phenyl-H), 2.67 (3H, s, isoxazole-CH_3), 2.48 (3H, s, phenyl-CH_3).

5 We wish to thank R. Suhr for a sample of this mixture.

6 Lang, Jr., S. A.; Lin, Y.-i. In Comprehensive Heterocyclic Chemistry; Katrizky, K. R.; Rees, C. W.; Potts,, K. T.; Eds.; Pergamon Press, Oxford: 1984; Vol 6, p 29.

7 **8**: IR (KBr) ν 2200 (nitrile),1793 (β–lactam) cm^{-1}. uV (EtOH) λ_{max} 249 (11,200) nm. FAB-MS, MH^+ = 464. ^1H NMR(300 MHz, $CDCl_3$) δ 7.94 (1H, d, NH), 7.34-6.96 (5H, phenyl-H), 6.00 (1H, dd, J = 5.0, 9.0 Hz, β-lactam-H), 5.96-5.88 (1H, m, allyl=CH), 5.60 (1H, d, J = 6.0 Hz, β-lactam-H), 5.37 (2H, m, allyl=CH_2), 4.69-4.55 (5H, m, 1/2 N-CH_2, allyl-CH_2, phenoxy-CH_2), 4.10 (1H, d, J = 18.0 Hz, 1/2 N-CH_2), 2.42 (3H,s, CH_3).

8 **13**: FAB-MS, MH^+ = 617. ^1H NMR (300 MHz $CDCl_3$) δ 7.95 (1H, d, J = 10.7 Hz, NH), 7.88 (2H, d, Ts-aromatic-H), 7.83 (1H, s pyrazole ring-H), 7.39 (2H, d, Ts-aromatic-H), 7.37-6.93 (5H, phenyl-H), 5.98-5.85 (2H, m, β-lactam-H, allyl=CH), 5.33 (2H, m, allyl=CH_2), 5.22 (1H, d, J = 4.9 Hz, β-lactam-H), 4.6 - 4.40 (5H, m, 1/2 N-CH_2, allyl-CH_2, phenoxy-CH_2), 4.00 (1H, d, J = 18.5 Hz, N-CH_2), 2.83 (3H, s, Ts-CH_3), 2.46 (s, 3H, pyrazole-CH_3).

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