# AZETIDINONE IMIDES

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Abstract - The synthesis of acetyl and Boc azetidinone imides is described.

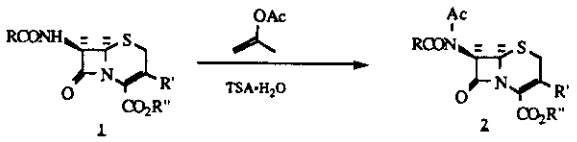
Recent interest[1,2] in the synthesis and use of diacylamino penicillins and cephalosporins prompts us to report our results in this area. Such imides are of interest not only from the standpoint of alpha-sulfoxide synthesis, but also as drugs or prodrugs and as protecting groups, for example, in preventing intramolecular cyclization leading to oxazoline azetidinone formation.

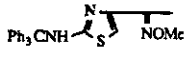
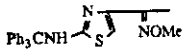
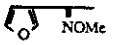
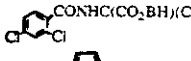
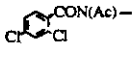
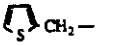
We have investigated two different approaches to β-lactam imides,[3] namely, the use of isopropenyl acetate-TSA·$H_2O$[toluenesulfonic acid monohydrate][4,5] to prepare acetyl imides and the use of $(Boc)_2O$-DMAP[4-dimethylaminopyridine][6,7] to prepare Boc imides.

Cephalosporin acetyl imides were readily prepared by refluxing (94°C) the corresponding amide in isopropenyl acetate containing TSA·$H_2O$ (~0.4 equiv.). When the reaction was complete, as indicated by tlc (1-18 h), the solvent was evaporated and the crude product chromatographed on silica gel to give pure acetyl imide. See Table I. Note in the case of the ceph C derivative and cefuroxime axetil that every available acyl NH is acetylated. Also note the use of the C-4 acid.

Use of the sulfoxide and sulfone was also studied where R, R' and R" equals $PhOCH_2$, $CH_3$, PNB. The sulfone gave acetyl imide in 56%, but required 8 h vs 2 h (99%) for the sulfide. Use of the sulfoxide resulted in a complex mixture, apparently due to Pummerer type reactions.

TABLE I

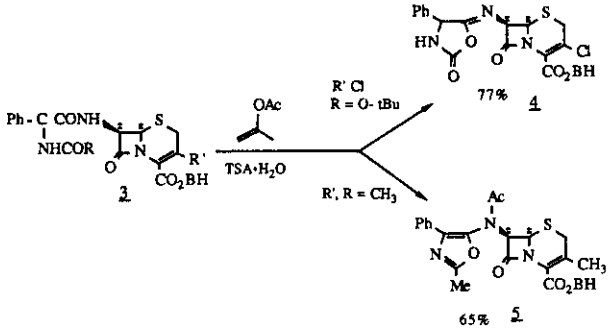



| R | R' | R" | R* | R'* | % |
|---|---|---|---|---|---|
| $PhOCH_2$ | $CH_3$ | PNB | | | 99 |
| $ClCH_2$ | $CH_3$ | PNB | | | 69 |
| $PhOCH_2$ | $CH_2OAc$ | BH | | | 98 |
| $PhOCH_2$ | Cl | BH | | | 60 |
| $CH_3$ | Cl | H | | | 74 |
| H | $CH_2OAc$ | BH | | | 74 |
|  | $CH_3$ | BH | | | 42 |
|  | $CH_2OAc$ | BH | | | 55 |
|  | $CH_2OC(O)NH_2$ | $CH(CH_2)OAc$ | | $CH_2O(CO)NAc_2$ | 34 |
|  | $CH_2OAc$ | BH |  | | 62 |
|  | Ac | BH | | | 78 |

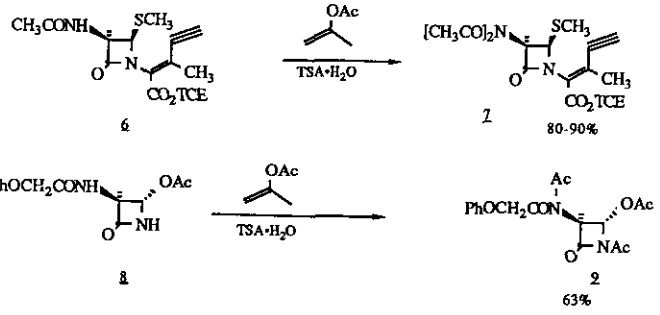
* same as starting material except as noted

PNB= p-nitrobenzyl, BH= benzhydryl

N-Acyl-D-phenylglycine cephem amides (3) formed cyclic products (4, 5) under these conditions.

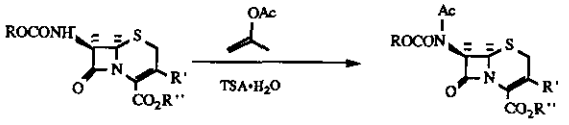



Several monocyclic azetidinones were also studied, thus the conversion of 6[8] to the bisacetyl imide 7 and the conversion of 4-acetoxyazetidinone 8 to 9.




Cephem C-7-carbamates also underwent the isopropenyl acetate acetylation, with the apparent exception of those containing an electron withdrawing group (trichloroethyl) in the carbamate moiety. See Table II.

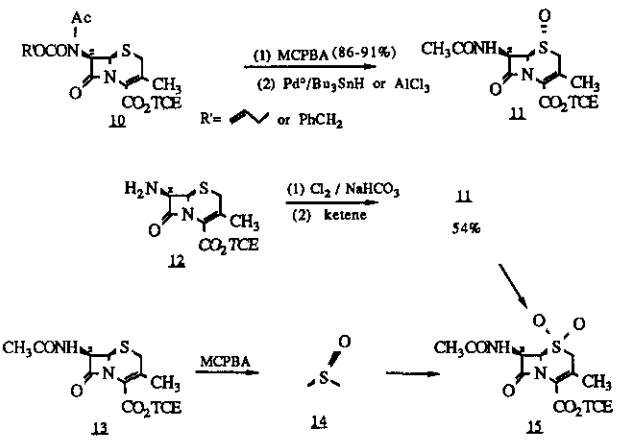
TABLE II




| R | R' | R" | % |
|---|---|---|---|
| $CH_3$ | $CH_3$ | TCE | >95* |
| TCE | $CH_3$ | $CH_3$ | 0 |
| $PhCH_2$ | $CH_3$ | TCE | 88 |
| $PhCH_2$ | $CH_3$ | PNB | 61 |
| TCE | Cl | PNB | 0 |
| allyl | $CH_3$ | TCE | 89 |
| allyl | $CH_3$ | $CH_3$ | 81 |

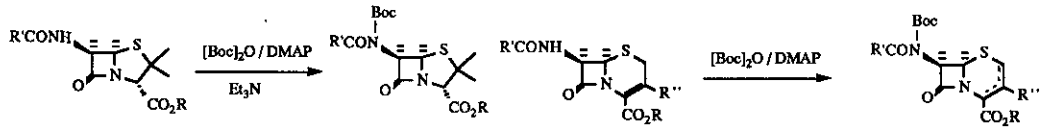
TCE = trichloroethyl, PNB = p-nitrobenzyl
* product has same Rf as starting material on tlc

m-Chloroperbenzoic acid oxidation of the cephem C-7-carbamate-acetyl imide sulfide (10) gave only one sulfoxide in 86-91% yield.[1] The stereochemistry of the sulfoxide was determined to be alpha by removal of the carbamate followed by direct comparison with authentic material prepared from the 7-amino-cephem ester (12) by chlorine-$NaHCO_3$ oxidation[9] followed by ketene acetylation. Note that chlorine-bicarbonate oxidation is a very convenient method of preparing alpha sulfoxide-7-amino cephem esters.



Alkyl amides of penicillins underwent degradation under isopropenyl acetate reaction conditions. Boc imides of penicillins and cephalosporins can be prepared, however, using $(Boc)_2O$-DMAP[6,7]. (See Table III.) The ratio of $\Delta^3$ to $\Delta^2$ cephems is apparently a function of the substrate and reaction time, with the $\Delta^3$ cephem predominating.

TABLE III

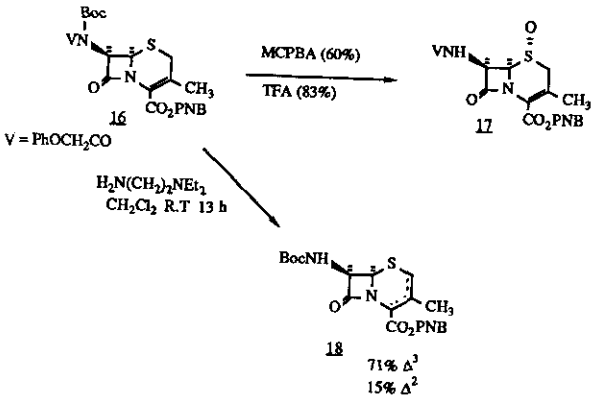


| | R' | R | % |
|---|---|---|---|
| | $PhCH_2$ | TCE | 80 |
| | $PhOCH_2$ | PNB | 66 |
| | allyl-O | BH | 62 |
| epi | $PhOCH_2$ | BH | 63 |

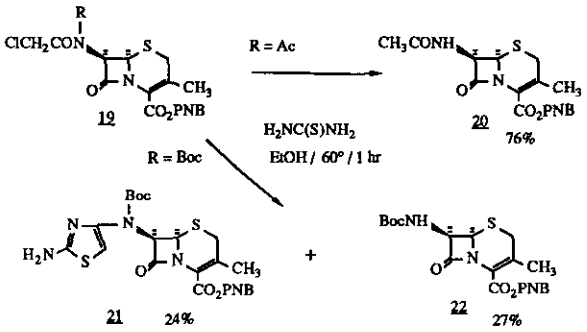
| R' | R | R" | % |
|---|---|---|---|
| $PhCH_2$ | $CH_3$ | $CH_3$ | 71 |
| $PhOCH_2$ | PNB | $CH_3$ | 60 |
| $CH_3$ | $CH_3$ | $CH_3$ | 64 |
| $ClCH_2$ | PNB | $CH_3$ | 38 |
| $CH_3O$ | PNB | $CH_3$ | 51 |
| H | BH | $CH_2OAc$ | 66 |
| allyl-O | TCE | $CH_3$ | 74 |
| $CH_3O$ | $CH_3$ | $CH_3$ | 71 |
| $CH_3$ | PNB | $CH_3$ | 71 |

*Oxidation of penicillin-G-Boc sulfide TCE ester with* MCPBA gave a mixture of α and β-sulfoxides (49% and 29%) similar to the results of Micetich[1]. Authentic penicillin-G-Boc-β-sulfoxide was prepared by reacting penicillin-G-β-sulfoxide ester with $(Boc)_2O$-DMAP to give the corresponding β-sulfoxide-Boc-imide (10-35%).

MCPBA oxidation of the cephalosporin V-Boc 16 gave a single sulfoxide, which on treatment with trifluoroacetic acid (TFA) gave the α-sulfoxide amide 17. Amide hydrolysis (86%) of the Boc-imide was accomplished using N,N-diethylethylenediamine[7].



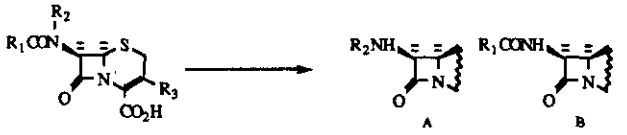

Thiourea hydrolysis[10] of the cephalosporin chloroacetyl imides in ethanol gave the corresponding amide 20 from the acetyl imide 19 (R=Ac), however, the Boc-imide 19 (R=Boc) gave in addition the aminothiazole derivative 21. Use of thiourea in water-THF, however, gave only 22 (90% crude).



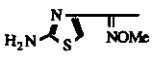

Hydrolysis studies were also undertaken on the cephalosporin imides at various pH in order to determine the imide stability and the nature of the hydrolysis product. Cephalosporin imides are much more susceptible to hydrolysis than the C-7-amide moiety where hydrolysis of the amide group is usually not observed when cephalosporins are studied in aqueous solution. The rates of hydrolysis of the individual N-acyl groups of the imide are influenced by both the electronic and steric effects of each acyl group. These effects may be seen in a series of imides where the structure of one of the N-acyl groups is kept constant, acetyl, and the other is a substituted acetic acid, $XCH_2CO$-(see Table IV).

TABLE IV

PSEUDO-FIRST ORDER RATES AND PRODUCTS OF IMIDE HYDROLYSIS

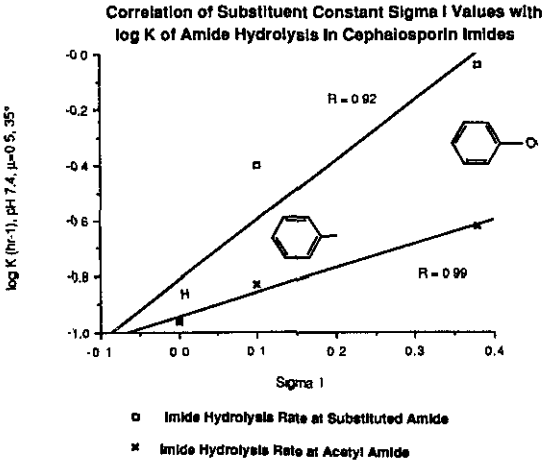


| | | | | K hydrolysis ($hr^{-1}$) 35°, μ = 0.5 | | % | |
|---|---|---|---|---|---|---|---|
| $R_1$ | $R_2$ | $R_3$ | pH | $R_1CON$ | $R_2N$ | A | B |
| $PhOCH_2$ | Ac | Cl | 7.4 | 0 90 | 0.24 | 79 | 21 |
| " | " | " | 6.0 | 0.066 | 0.013 | 84 | 16 |
| " | " | " | 4.0 | 0.031 | 0 0030 | 91 | 9 |
| $PhCH_2$ | Ac | Cl | 7.4 | 0.40 | 0.15 | 73 | 27 |
| $CH_3$ | Ac | Cl | 7.4 | 0.055 | 0 055 | 50 | 50 |
| " | " | " | 6 0 | 0.0035 | 0.0035 | 50 | 50 |
| ATMO | Ac | $CH_2OAc$ | 7.4 | ~0 | 1.14 | <1 | >99 |
| " | " | " | 6 0 | ~0 | 0.12 | <1 | >99 |
| " | " | " | 4 0 | ~0 | 0.084 | <1 | >99 |
| H | Ac | $CH_2OAc$ | 7 4 | 3.71 | 0.24 | 94 | 6 |
| $PhOCH_2$ | Boc | $CH_3$ | 9.0 | 4.24 | 0.75 | 85 | 15 |
| " | " | " | 8.0 | 0.51 | 0 51 | 50 | 50 |
| " | " | " | 7.4 | 0.20 | 0.56 | 26 | 74 |
| " | " | " | 4.0 | 0.03 | 0 58 | 5 | 95 |

ATMO = 

At pH 7.4 for the series X equals H, $C_6H_5$-, and $C_6H_5O$- the rate of hydrolysis of both the substituted acetyl amide and the acetyl amide of the imide correlate with the $\sigma_I$ value of the substituent. The substituent effect is greater on the rate of hydrolysis of the substituted amide because of the proximity of that carbonyl carbon to the substituent. See Figure I. For the case of $R_1$ being ATMO, a $\sigma_I$ value is unavailable, hydrolysis occurs exclusively at the acetyl amide. We presume this is due to steric reasons similar to those observed by Lamberton[11] with ortho vs meta and para substituents on N-acylbenzanilides. Similarly, when formyl is compared with acetyl amide (an N-acetyl group common to both imides) the rate of imide hydrolysis is increased 36 fold with predominate hydrolysis occurring at the formyl amide.

FIG. I



When imide hydrolyses are carried out at a series of pH it becomes apparent that the rates of hydrolysis of the individual acyl amides respond to the changes in pH differently. For example, the mixed imide composed of V and N-t Boc gives predominantly one product depending on whether the hydrolysis is done at pH 4 or 9. In this case the rate of hydrolysis of the N-t-Boc is relatively constant over the pH range, whereas the rate of hydrolysis of the N-phenoxyacetic acid amide changes over 100 fold.

MIC data obtained on most of the diacylamino cephalosporin acids were identical to the microbiological activity of the major cephalosporin hydrolysis product. The only exception was the bis-N-acetyl-3-Cl cephem, where significantly less microbiological activity was observed after 18 h. Since the hydrolysis half life of most of the imides was in the range of 6 to 9 h at the pH of the test agar, pH 6, all of the microbiological activity could be accounted for by the formation of significant amounts of hydrolysis product. The fact that the bis-N-acetyl-3-Cl-cephem imide had significantly less activity than its hydrolysis product is consistent with the hypothesis that the imides lack microbiological activity, since the stability of this imide at the pH of the test agar ($T_{\frac{1}{2}}$ of 63 h) would preclude the formation of significant amounts of microbiologically active N-acetyl-3-Cl cephem during the assay.

## EXPERIMENTAL

The following instruments were used for obtaining the spectral data: $^1$H nmr: Varian T-60, G.E. QE-300; ir spectra: Perkin Elmer 281; mass spectral data: Varian-m.a.t.-731. The hydrolysis rates were determined by following the loss of the parent imide by HPLC. Presence of the imide hydrolysis products was confirmed by spiking HPLC samples of the reaction solution with the authentic cephalosporins. The amount of each product was quantitated by HPLC to determine the relative hydrolysis rates of the two amide groups. The stationary phase was a 4.6 X 250 mm Zorbax ODS (Dupont) reverse-phase column with the variable-wavelength detector set at 254 nm. The flow rate was 1 ml/min. The mobile phase contained acetonitrile/0.025M $NH_4OAc$ ranging from 38:62 to 3:97, v/v as needed. All rates were determined at constant pH on a pH-stat, adding NaOH or HCl as necessary to maintain pH. Experiments were carried out at 35°C. The ionic strength was adjusted to 0.5 with potassium chloride. Initial imide concentrations were 1 X $10^{-3}$M.

*4-Nitrobenzyl-(7β)-3-methyl-7-[N-chloroacety-N-acetyl amino]-3-cephem-4-carboxylate*, 19 (R=Ac). The chloroacetyl amide (0.745 g, 1.75 mM) was combined with 25 ml of isopropenyl acetate and 0.4 equiv. (0.133 g) toluenesulfonic acid monohydrate and gently refluxed 2 h. It was then

evaporated to dryness and chromatographed on silica gel using toluene-ethyl acetate gradient to give 569 mg of product (69%) as a froth; m/z 467; ir ν ($CHCl_3$) 1780 $cm^{-1}$(β-lactam); nmr ($CDCl_3$) δ 2.30 (s, 3, Me), 2.43 (s, 3, Ac), 3.07, 3.55 (AB, J=16 Hz, 2, C(2) protons), 4.67 (s, 2, Cl-$CH_2$), 5.10 (d, J=4 Hz, 1, $H^6$), 5.3-5.4 (m, 3, $H^7$, PNB), 7.60, 8.23 (AB, J=8 Hz, 4, PNB).

4-Nitrobenzyl-(7β)-3-methyl-7-acetamido-3-cephem-4-carboxylate, 20.

*The imide 19 (0.569 g, 1.22 mM) was dissolved in 2 ml of $CH_2Cl_2$ plus 35 ml of EtOH.* To this was added 2.0 equiv. (0.185 g) thiourea, and the mixture was heated at 60°C for 1 h. The resulting white slurry was evaporated to dryness, then taken up in $CH_2Cl_2$ and washed with 4x $H_2O$, 1x brine, dried ($Na_2SO_4$) and evaporated to give 360 mg of product (76%) as a white solid. Nmr and tlc were identical to authentic material.

Trichloroethyl-(6β)-6-[N-phenylacetyl-N-t-butoxycarbonylamino]-penam-3-carboxylate.

A solution of Pen G-TCE (0.466 g, 1.0 mM), 2.0 equiv. (0.436 g) of $(Boc)_2O$, 1.0 equiv. (0.122 g) DMAP and 1.0 equiv. (0.14 ml) $Et_3N$ in 20 ml $CH_2Cl_2$ was allowed to stir at room temperature for 1 h. The solution was washed with cold 1N HCl, brine and then dried ($Na_2SO_4$), evaporated to dryness and chromatographed on silica gel using toluene-ethyl acetate gradient to give 451 mg (80%) product as a froth; m/z 566; ir ν ($CHCl_3$) 1790 $cm^{-1}$ (β-lactam); nmr ($CDCl_3$) δ (1.54 s, 9, t-Bu), 1.57 (s, 3, Me), 1.75 (s, 3, Me), 4.19 (s, 2, benzyl), 4.64 (s, 1, C(3) proton), 4.72, 4.89 (AB, 2, J=12 Hz, TCE), 5.50 (d, J=4 Hz, 1, $H^5$), 5.60 (d, J=4 Hz, 1, $H^6$), 7.3 (m, 5, phenyl).

4-Nitrobenzyl-(7β)-3-methyl-7[N-phenoxyacetyl-N-t-butoxycarbonylamino]-3-cephem-4-carboxylate, 16.

A solution of DCV-PNB amide (0.458 g, 0.947 mM), 2.0 equiv. (0.413 g, 1.89 mM) of $(Boc)_2O$, 1.0 equiv. (0.116 g) of DMAP and 1.0 equiv. (0.13 ml) of $Et_3N$ in 20 ml $CH_2Cl_2$ was allowed to stir at room temperature for 1 h. It was then washed with cold 1N HCl, brine, dried ($Na_2SO_4$), evaporated to dryness and chromatographed on silica gel using a toluene-ethyl acetate gradient to give 335 mg (60%) of product; m/z 583; ir ν ($CHCl_3$) 1765 $cm^{-1}$ (β-lactam); nmr ($CDCl_3$) δ 1.56 (s, 9, t-Bu), 2.24 (s, 3, Me), 3.2, 3.4 (AB, J=16 Hz, 2, C(2) protons - $H^7$ to $H^2$-β[5-bond coupling]), 5.06 (d, J=4 Hz, 1, $H^6$), 5.21 (s, 2, $PhOCH_2$), 5.31, 5.44 (AB, J=13 Hz, 2, PNB), 5.83 (bd, J=4 Hz, 1, $H^7$), 6.9, 7.3 (m, 5, phenoxy), 7.64, 8.25 (AB J=9Hz, 4, PNB).

4-Nitrobenzyl-(7β)-3-methyl-7-[N-t-butoxycarbonylamino]-2 and 3-Cephem-4-carboxylate, 18.

A solution of the Boc imide 16 (0.584 g, 1.0 mM) and 1.0 equiv. (0.116 g) of N,N-diethyletylene-

diamine in 30 ml of $CH_2Cl_2$ was allowed to stir at room temperature for 13 h. It was washed with cold 1N HCl, brine, dried ($Na_2SO_4$), evaporated and chromatographed on silica gel using a toluene-ethyl acetate gradient to give 319 mg of product as $\Delta^3$ and 70 mg as $\Delta^2$; $\Delta^3$-product-m/z 449; ir ν 1770 $cm^{-1}$ (β-lactam); nmr ($CDCl_3$) δ 1.49 (s, 9, t-Bu), 2.20 (s, 3 Me), 3.29, 3.58 (AB, J=18 Hz, 2, C(2) protons), 4.99 (d, J=4 Hz, 1, $H^6$), 5.3-5.5 (m, 3, PNB, NH), 5.61 (dd, J=4, 9 Hz, $H^7$).

$\Delta^2$-product-ir ν ($CHCl_3$) 1770 $cm^{-1}$(β-lactam); nmr ($CDCl_3$) δ 1.47 (s, 9, t-Bu), 1.86 (s, 3, Me), 4.83 (bs, 1, $H^4$), 5.2-5.6 (m, $H^6$, $H^7$, PNB), 5.97 (bs, 1, $H^2$), 7.58, 8.28 (AB, J=8 Hz, 4, PNB).

4-Diphenylmethyl-(7β)-[2-oxo-4-phenyl-5-oxazolidinylideneamino]-3-chloro-3-cephem-4-carboxylate 4; m/z 560; ir ν ($CHCl_3$) 1780 $cm^{-1}$; nmr ($CDCl_3$) δ 3.14, 3.66 (AB J=16 Hz, 2, C(2) protons), 4.94 (d, J=4 Hz, 1, $H^6$), 4.94 (s, 1, NH), 5.40 (d, J=4 Hz, 1, $H^7$).

4-Diphenylmethyl-(7β)-[N-2-methyl-4-phenyl-5-oxazoylyl-N-acetylamino]-3-methyl-3-cephem-4-carboxylate 5; m/z 579; ir ν ($CHCl_3$) 1775 $cm^{-1}$; nmr ($CDCl_3$) δ 2.26 (s, 3, C(3) methyl), 2.40 (m, 6, Ac, oxazole-Me), 2.90, 3.58 (AB, J=14 Hz, 2, C(2) protons), 4.98 (d, J=4 Hz, 1, $H^6$), 5.28 (d, J=4 Hz, 1, $H^7$).

Cis-3-(diacetylamino)-α-(1-methyl-2-propynylidene)-2-(methylthiol)-4-oxo-1-azetidineacetic acid trichloroethyl ester 7; nmr ($CDCl_3$) δ 2.09 (s, 3, SMe), 2.50 (s, 9, $N(Ac)_2$, vinyl Me), 3.90 (s, 1, acetylene proton), 4.80, 5.05 (AB, J=11 Hz, 2, TCE), 5.50 (d, J=4 Hz, 1, $H^2$), 5.67 (d, J=4 Hz, 1, $H^3$).

Trans-N-acetyl-N-[1-acetyl-2-(acetoxy)-4-oxo-3-azetidinoyl]-2-phenoxyacetamide 9; m/z 362; ir ν ($CHCl_3$) 1810 $cm^{-1}$; nmr ($CDCl_3$) δ 2.17 (s, 3, C(2)-OAc), 2.43 (s, 6, NAc), 4.97 (d, J=2 Hz, 1, $H^3$), 5.10 (s, 2, $PhOCH_2$), 6.37 (d, J=2 Hz, 1, $H^2$).

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