# *N*-ACYL 3-ALKYLIDENYL- AND 3-ALKYL AZETIDIN-2-ONES: A NEW CLASS OF MONOCYCLIC β-LACTAM ANTIBACTERIAL AGENTS

## 1. STRUCTURE-ACTIVITY RELATIONSHIPS OF 3-ISOPROPYLIDENE AND 3-ISOPROPYL ANALOGS†

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The synthesis and antibacterial activity of a series of *N*-acyl 3-isopropylidenyl- and 3-isopropyl 2-azetidinones having potent *in vitro* antibacterial activity, particularly against anaerobic organisms, is described. A distinguishing structural feature of these compounds is the lack of any ionizable moiety appendant to the lactam nitrogen.

In our search for novel synthetic antibacterial agents, we sought to explore the potential utility of a monocyclic β-lactam doubly-activated by an exocyclic C-C double bond at position C-3, and an appropriate electron-withdrawing moiety on the lactam N-1 nitrogen. The rationale behind this template design hinged on the rudimentary concept of creating additional ring strain through the juxtapositioning of two $sp^2$-hybridized carbons within the 4-membered ring. It was envisioned that such ring strain, in concert with the electron-withdrawing effect of an appropriate N-1 substituent, might serve to sufficiently activate the β-lactam carbonyl as an electrophile, thereby potentially allowing for acylation of an active site serine hydroxyl in the targeted transpeptidases involved in microbial cell wall biosynthesis.[4,5]

The provision of a sufficient chemical reactivity to any particular β-lactam carbonyl does not, however, in and of itself render antibacterial activity.[6,7] The β-lactam must also be fitted with appropriate structural appendages that allow for, or facilitate the binding of, the electrophile at the active site.[8,9] In order to address this regard, at the outset of this lead-finding program we selected for synthesis both the *Z* and *E* isomers of 3-(1-methyl-2-hydroxyethylidene)-2-azetidinone[10] (the latter comprising the lactam portion of the carbapenem asparenomycins).[11,12] Such hydroxyisopropylidenyl templates, equipped with a readily manipulable synthetic handle, could be exploited to generate a multitude of structurally-varied entities at C-3, with the objective of optimization of biological activity. Subsequently we discovered that the "parent" *N*-acyl C-3 unsubstituted isopropylidenes (**a**, Schemes 1 and 2) and their corresponding dihydro analogs, the *N*-acyl 3-isopropyl azetidin-2-ones (**b**), exhibited the highest potencies of this class. Here we report on the structure-activity relationships (SAR) of these unusual β-lactam antibacterial agents.

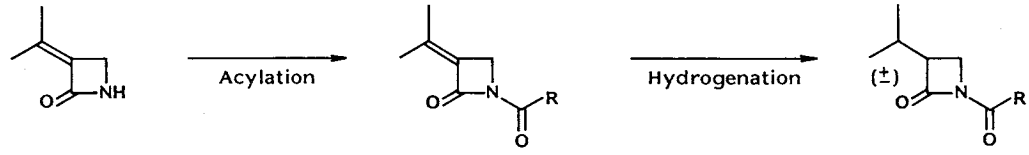
### Results and Discussion

#### Chemistry

We have previously described the chemistry employed in the synthesis of the requisite 3-isopropylidenyl

† The content of this paper has been presented in part, see references 1～3.

Scheme 1. *N*-Alkanoyl 3-isopropylidene (**a**) and 3-isopropyl (**b**) 2-azetidinones.

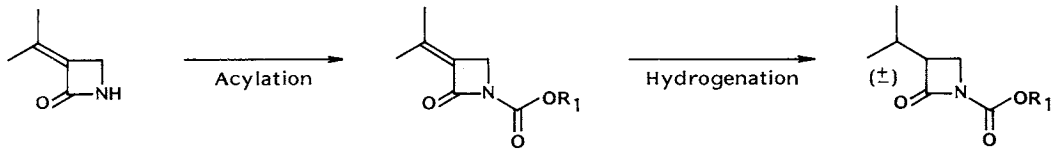



**1** **a** **b**

| Method of acylation | Compound | Alkanoyl side chain R | Compound |
|---|---|---|---|
| A | **2a** | $-CH_3$ | **2b** |
| A | **3a** | $-(CH_2)_2CH_3$ | **3b** |
| A | **4a** | $-(CH_2)_3CH_3$ | **4b** |
| A | **5a** | $-(CH_2)_4CH_3$ | **5b** |
| B | **6a** | $-(CH_2)_6CH_3$ | **6b** |
| B | **7a** | $-(CH_2)_8CH{=}CH_2$ | — |
| — | — | $-(CH_2)_9CH_3$ | **8b**[a] |
| C | **13a** | $-CH_2OCH_2CH_3$ | **13b** |
| C | **14a** | $-(CH_2)_3OCH_3$ | **14b** |
| C | **15a** | $-(CH_2)_4OCH_2Ph$ | **15b** |
| — | — | $-(CH_2)_4OH$ | **16b** |
| C | **17a** | $-(CH_2)_2COCH_3$ | **17b** |
| C | **18a** | $-(CH_2)_4CO_2CH_3$ | **18b** |

[a] Hydrogenation of **7a** gives directly **8b**.

Scheme 2. *N*-Carboxylic acid ester analogs.




**1** **a** **b**

| Compound | Ester side chain $R_1$ | Compound |
|---|---|---|
| **9a** | $-CH_2CH_3$ | **9b** |
| **10a** | $-(CH_2)_2CH_3$ | **10b** |
| **11a** | $-(CH_2)_3CH_3$ | **11b** |
| **12a** | $-(CH_2)_2OCH_3$ | **12b** |

2-azetidinone **1** and the above described hydroxyisopropylidene templates.[10] Acylation of **1** to give compounds in the **a** series was carried out using either the appropriate carboxylic acid anhydride and dimethylaminopyridine (DMAP) in pyridine (Method A), the acid chloride and triethylamine in methylene chloride (Method B), or the carboxylic acid and dicyclohexylcarbodiimide in tetrahydrofuran (Method C). Thus we obtained the "alkanoyl-activated" *N*-acyl 3-alkylidene 2-azetidinones **2a**~**7a** and **13a**~**18a** which were generally isolated as colorless oils upon silica gel chromatography (Scheme 1).

The "ester-activated" analogs **9a**~**12a** were derived by the coupling of **1** with excess chloroformate (to effect a reasonable degree of conversion) in the presence of triethylamine and DMAP in methylene chloride (Scheme 2).

Catalytic hydrogenation of the alkylidene azetidinones **2a**～**18a** using palladium black or 10% palladium on charcoal catalyst (1 atm hydrogen, ethyl acetate) cleanly provided in excellent yields the corresponding racemic *N*-acyl 3-isopropyl azetidin-2-one analogs **2b**～**18b**. The *N*-(5-hydroxypentanoyl) 3-isopropyl analog **16b** was obtained upon acid-catalyzed hydrogenolysis of benzyl ether **15b**.†

*In Vitro* Antibacterial Activity

Table 1 gives the zones of inhibition for all susceptible organisms, for the *N*-acyl 3-isopropylidene- and 3-isopropyl azetidin-2-ones, as determined by a standard agar diffusion assay. Extremely large zones of inhibition were observed upon dipped-disk assay for those compounds lacking additional heteroatoms within the N-1 alkanoyl chain. Against all susceptible organisms, the optimal chain length of these simple alkanoyl substituted analogs (**2a**, **2b**～**7a**, **8b**) was a length of 5～6 carbons. The *N*-pentanoyl **4b** and *N*-hexanoyl **5b** analogs exhibited some of the most dramatically-large zones. When **5b** was tested at a solution concentration of 1 mg/ml (approx 80 μg/12.7 mm disk) against *Bacteroides fragilis* UC 6513, a zone of 154 mm diameter was observed; at 1,000-fold lower loading (80 ng/disk), a 30-mm zone of inhibition was obtained. Such uncharacteristically-immense zones were also observed against *Clostridium perfringens* UC 6509, and a number of Gram-positive facultative organisms, including the multiply-resistant strain *Staphylococcus aureus* UC 6685.

These lipophilic compounds exhibited a marked atypical zone size-minimum inhibitory concentration (MIC) correlation. In general, only those analogs producing zones of inhibition >50 mm at 80 μg/disk exhibited correspondingly low MIC values (Tables 1 and 2). No Gram-negative aerobe activity was observed for any member of this class. The poor MIC results for all compounds vs. *C. perfringens* may be associated with the presence of resistant colonies within the large zones of inhibition, which was observed for a number of analogs.

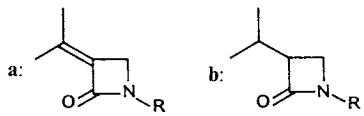
The highly lipophilic nature of compounds **2a**, **2b**～**11a**, **11b** is reflected in the low aqueous solubilities, particularly of the analogs with aliphatic chains like **5b** (<1 mg/ml). In order to generate more water-soluble compounds, without resorting to the introduction of a charged group, we synthesized a series of analogs having 1～2 oxygen atoms incorporated into the *N*-acyl chain (**12a**, **12b**～**18a**, **18b**). Several of the compounds showed greatly improved water solubility, *e.g.*, methoxy ether **12a** (20 mg/ml), and methyl ketone **17a** (7 mg/ml). For these more soluble analogs, somewhat more typical zone size-MIC correlations were observed.

In our systematic substitution of oxygen for $CH_2$ units within the *N*-acyl chain, we discovered analog **10a**, which has the highest overall *in vitro* potency (Table 2). This propyl ester-activated 3-isopropylidene azetidin-2-one is unlike any other congener, in that **10a** was 2～8 times more potent than its corresponding isopropyl analog **10b**. Homologous esters in the ethyl (**9a** and **9b**) and butyl (**11a** and **11b**) series were significantly less active than **10a**.

The highest *in vitro* activity of these compounds is found vs. anaerobes of the *Bacteroides* species (Table 2). Analog **10a** is extremely potent vs. *Bacteroides thetaiotaomicron* UC 9014 and UC 6611, and *B. fragilis* UC 9370, compared with clindamycin. *N*-(Ethoxyacetyl) 3-isopropylidene **13a** was comparable in activity to clindamycin vs. three *B. fragilis* strains, and showed moderate activity vs. *Staphylococcus epidermidis* UC 30033. Both **10a** and **10b**, as well as the methoxy (**14b**) and benzyloxy (**15b**) alkanoyl-activated 3-isopropyl analogs exhibited weak activity vs. *S. aureus* UC 9218 and UC 9271 and/or

† No attempt was made to prepare enantiomerically pure 3-isopropyl analogs.

Table 1. Zones of inhibition (diameter mm, 1 mg/ml, ~80 μl/12.7 mm disk).




| Compound | R | Organisms | | | | | |
|---|---|---|---|---|---|---|---|
| | | *Bf* | *Cp* | *Sa* 6685 | *Sa* 3665 | *Sepi* | *Sp* |
| **2a** | $-COCH_3$ | >90[a] | 62 | 0 | 0 | 0 | 13[d] |
| **2b** | $-COCH_3$ | >86[a] | 57 | Tr | 0 | 8[d] | 0 |
| **3a** | $-CO(CH_2)_2CH_3$ | >90 | 62 | 12[d] | NT | Tr | 0 |
| **3b** | $-CO(CH_2)_2CH_3$ | 140 | 81RC | 30[c,d] | 24[c] | 11[d] | 13H[d] |
| **4a** | $-CO(CH_2)_3CH_3$ | 110 | 80 | 38[d] | 39 | 30[d] | 21[d] |
| **4b** | $-CO(CH_2)_3CH_3$ | 166[b] | 76RC | 70[c,d] | 62 | 53[d] | 0 |
| **5a** | $-CO(CH_2)_4CH_3$ | 113 | 92RC | 50[d] | 30 | 39[d] | Tr |
| **5b** | $-CO(CH_2)_4CH_3$ | 154 | 105RC | 77[d] | 44[a] | 67[d] | Tr |
| **6a** | $-CO(CH_2)_6CH_3$ | 90 | 54 | 28[d] | 21 | 13[d] | 11[d] |
| **6b** | $-CO(CH_2)_6CH_3$ | 148 | 71 | 48[d] | 36 | 46[d] | 8[d] |
| **7a** | $-CO(CH_2)_8CH=CH_2$ | 43 | 24H | 8[d] | 0 | Tr | 0 |
| **8b** | $-CO(CH_2)_9CH_3$ | 57 | 23H | 15[d] | 15H | 11[d] | 0 |
| **9a** | $-CO_2CH_2CH_3$ | 60 | 53 | 32 | 21 | 0 | 0 |
| **9b** | $-CO_2CH_2CH_3$ | 58 | 45 | 25 | 17 | 0 | 0 |
| **10a** | $-CO_2(CH_2)_2CH_3$ | 60 | 57 | 49 | 34 | 26H | 0 |
| **10b** | $-CO_2(CH_2)_2CH_3$ | 66 | 49 | 52 | 27 | 28H | 0 |
| **11a** | $-CO_2(CH_2)_3CH_3$ | 77 | 49RC | 30[d] | 29 | 25H | 15[d] |
| **11b** | $-CO_2(CH_2)_3CH_3$ | 80 | 43RC | 31[d] | 30 | 33[d] | 10[d] |
| **12a** | $-CO_2(CH_2)_2OCH_3$ | 39 | 35 | 27 | 21 | 0 | NT |
| **12b** | $-CO_2(CH_2)_2OCH_3$ | 38 | 31 | 32 | 22 | 22 | 0 |
| **13a** | $-COCH_2OCH_2CH_3$ | 52 | 45 | 39 | 30 | 27 | 0 |
| **13b** | $-COCH_2OCH_2CH_3$ | 47 | 40 | 38 | 33 | 32 | 0 |
| **14a** | $-CO(CH_2)_3OCH_3$ | 47 | 41 | 28 | 19 | 20H | 0 |
| **14b** | $-CO(CH_2)_3OCH_3$ | 48 | 35 | 34 | 26 | 27H | 0 |
| **15a** | $-CO(CH_2)_4OCH_2Ph$ | 39 | 32 | 20 | 15 | 15 | 0 |
| **15b** | $-CO(CH_2)_4OCH_2Ph$ | 45 | 29 | 33 | 25 | 25 | 0 |
| **16b** | $-CO(CH_2)_4OH$ | 49 | 25 | 30 | 29S | 25 | 0 |
| **17a** | $-CO(CH_2)_2COCH_3$ | 40 | 33 | 17 | 14 | 0 | 0 |
| **17b** | $-CO(CH_2)_2COCH_3$ | 41 | 21H | 24 | 15 | 19H | 0 |
| **18a** | $-CO(CH_2)_4CO_2CH_3$ | 39 | 34 | 22 | 15 | 19H | 0 |
| **18b** | $-CO(CH_2)_4CO_2CH_3$ | 43 | 29 | 31 | 25 | 24 | 0 |

Abbreviations: *Bf*, *Bacteroides fragilis* UC6513; *Cp*, *Clostridium perfringens* UC6509; *Sa* 6685, *Staphylococcus aureus* UC6685; *Sa* 3665, *S. aureus* UC3665; *Sepi*, *Staphylococcus epidermidis* UC719; *Sp*, *Streptococcus pneumoniae* UC9207; Additional organisms [compound (zone, mm)]: *Streptococcus pyogenes* UC6055: **6a** (16), **6b** (15), **8b** (21), *Streptococcus faecalis* UC241; **16b** (32); *Penicillium oxalicum* UC1268: **4a** (17H), **5a** (17H), **5b** (17H), **8b** (18), **11b** (17H); Tr, trace; H, hazy zone; RC, resistant colonies present; NT, not tested.

[a] Tested at 0.1 mg/ml (~8 μg/disk).

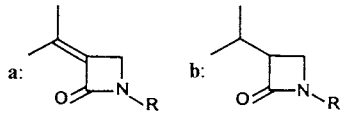
[b] When tested at 0.1 mg/ml, zone was 126 mm.

[c] Averaged dimensions of oblong zone.

[d] 6.5 mm disk used.

*S. epidermidis* UC 30033. Butyl ester-activated analogs **11a** and **11b** had the highest activity vs. *S. epidermidis* UC 30031. While the *N*-hexanoyl isopropyl analog **5b** also exhibited potent activity vs. anaerobes, against *S. aureus* strains (UC 6675, UC 3665, and UC 6685), significant, but only partial inhibition was effected at low levels (4 μg/ml). For these strains, partial growth at higher drug levels was observed upon close visual examination, evidenced by the presence of two or more colonies, and

Table 2. *In vitro* antibacterial activity (MIC, μg/ml) of *N*-acyl 3-isopropylidene and 3-isopropyl 2-azetidinones.




| Compound | R | Organisms | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Bth*1 | *Bth*2 | *Bf*1 | *Bf*2 | *Cp* | *Sa*1 | *Sa*2 | *Se* | *Sf* | *Sp* | *Ec* | *Kp* | *Psa* |
| **5b** | $CO(CH_2)_4CH_3$ | 1 | NT | 2 | 8[c] | >128 | >256 (4)[a] | >256 (4)[a] | NT | >64 | 128 | >256 | >256 | >256 |
| **9a** | $CO_2C_2H_5$ | 1 | 1 | 4 | 16 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **9b** | $CO_2C_2H_5$ | 1 | 2 | 8 | 8 | >64 | 64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **10a** | $CO_2C_3H_7$ | 0.125 | 0.5 | 1 | 4 | >64 | 32 | 32 | 64 | >64 | 128 | >64 | >64 | >64 |
| **10b** | $CO_2C_3H_7$ | 1 | 2 | 4 | 8 | >64 | 32 | 64 | 128 | >64 | >64 | >64 | >64 | >64 |
| **11a** | $CO_2C_4H_9$ | 4 | 4 | 4 | 4 | >64 | >64 | >64 | 32[b] | >64 | >64 | >64 | >64 | >64 |
| **11b** | $CO_2C_4H_9$ | 4 | 4 | 4 | 4 | >64 | 64 | 64 | >64[b] | >64 | 256 | >64 | >64 | >64 |
| **12a** | $CO_2(CH_2)_2OCH_3$ | 32 | 32 | 32 | 32 | >64 | 64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **12b** | $CO_2(CH_2)_2OCH_3$ | 16 | 16 | 16 | 32 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **13a** | $COCH_2OC_2H_5$ | 2 | 2 | 1 | 2 | >64 | >64 | >64 | 16 | >64 | >64 | >64 | >64 | >64 |
| **13b** | $COCH_2OC_2H_5$ | 16 | 16 | 16 | 16 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **14a** | $CO(CH_2)_3OCH_3$ | 8 | 8 | 16 | 32 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **14b** | $CO(CH_2)_3OCH_3$ | 2 | 4 | 8 | 32 | >64 | 32 | >64 | 32 | >64 | >64 | >64 | >64 | >64 |
| **15a** | $CO(CH_2)_4OCH_2Ph$ | 16 | 16 | 8 | 8 | >64 | 128 | 128 | 128 | >128 | 128 | >64 | >64 | >64 |
| **15b** | $CO(CH_2)_4OCH_2Ph$ | NT | NT | NT | NT | NT | 32 | >64 | 32 | >64 | >64 | >64 | >64 | >64 |
| **16b** | $CO(CH_2)_4OH$ | 2 | 16 | 16 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **17a** | $CO(CH_2)_2COCH_3$ | 16 | 16 | 16 | 32 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **17b** | $CO(CH_2)_2COCH_3$ | 16 | 16 | 16 | 16 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **18a** | $CO(CH_2)_4CO_2CH_3$ | >64 | 64 | 64 | 64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 | >64 |
| **18b** | $CO(CH_2)_4CO_2CH_3$ | 8 | 8 | 8 | 8 | >64 | >64 | 64 | >64 | >64 | >64 | >64 | >64 | >64 |
| Cefoxitin | | 32 | 16 | 8 | 4 | 4 | 4 | 4 | 16 | >64 | 4 | 4 | 4 | >128 |
| Clindamycin | | 2 | 1 | 1 | ≤0.03 | 0.06 | ≤0.125 | ≤0.125 | ≤0.125 | >64 | ≤0.125 | >128 | 128 | >128 |
| Aztreonam | | NT | NT | >128 | 128 | 256 | >128 | NT | >128 | >128 | 128 | 0.06 | 0.06 | 2 |

Abbreviations: *Bth*1, *Bacteroides thetaiotaomicron* UC9014; *Bth*2, *B. thetaiotaomicron* UC6611; *Bf*1, *Bacteroides fragilis* UC9370; *Bf*2, *B. fragilis* UC6513; *Cp*, *Clostridium perfringens* UC6509; *Sa*1, *Staphylococcus aureus* UC9218; *Sa*2, *S. aureus* UC9271; *Se*, *Staphylococcus epidermidis* UC30033; *Sf*, *Streptococcus faecalis* UC9217; *Sp*, *Streptococcus pneumoniae* UC41; *Ec*, *Escherichia coli* UC6674; *Kp*, *Klebsiella pneumoniae* UC30090; *Psa*, *Pseudomonas aeruginosa* UC6676; NT, not tested.

[a] Significant (but incomplete) inhibition of inoculum from value in parenthesis to highest concentration tested.

[b] *S. epidermidis* UC30031 MIC = 4 μg/ml.

[c] *B. fragilis* UC6428 MIC = 2 μg/ml.

thus preventing assignment of the lower endpoint as the MIC.

### *In Vivo* Activity

None of the compounds tested *in vivo* at levels up to 50 mg/kg elicited a reproducible therapeutic response in mice experimentally-infected with either *S. epidermidis* UC 12084, *S. aureus* UC 9271 or UC 6685, when administered orally or subcutaneously. The compounds were not tested *in vivo* against anaerobic bacteria.

### Conclusions

It is to be noted that a prevalent structural feature of these *N*-acyl 3-alkylidenyl and 3-alkyl 2-azetidinones is that these are non-ionizable molecules, devoid of any charged appendage about the N-1 nitrogen, as will be found to date in all other $\beta$-lactam antibiotics exhibiting significant *in vitro* potency levels.[13~15] As such, these interesting synthetic substances can be considered as comprising a new class of monocyclic $\beta$-lactam antibacterial agents.

Whatever degree of activation the $\beta$-lactam carbonyl is afforded from the strain induced by the appendage of a double bond exocyclic to the ring, the net electrophilicity is attenuated as a consequence of resonance bonding of the conjugated system.[16] This is evident upon examination of the respective IR frequencies of any **a**/**b** analog pair having an identical N-1 group: the 3-isopropyl azetidinone carbonyl always has a higher energy stretching frequency (approximately 10 $cm^{-1}$) than that of the corresponding isopropylidene analog. Thus the dihydro **b** analog apparently possesses the more chemically-reactive carbonyl,[6,17] which may be reflected in the biological results. In all cases, save the previously noted **10a**, the isopropyl **b** congener is the more active of any given **a**/**b** pair having identical N-1 substituents. *N*-Acyl substitution alone is therefore sufficient to induce a high degree of chemical reactivity to 3-alkyl 2-azetidinones.[18] This has also subsequently been demonstrated by THOMAS and WILLIAMS,[19] where they activated a 3,3,4-trialkyl-substituted 2-azetidinone toward intramolecular ring opening by acylation on nitrogen, for the purpose of constructing the $\delta$-lactone fragment of the lankacidins. Hence our rationalized dual requirements of augmented ring strain and electronic withdrawal have proven overly exacting.

Any correlation of antibacterial potency with IR carbonyl stretching frequencies without consideration of the differential stereochemical biases involved upon binding an essentially planar 3-isopropylidene $\beta$-lactam molecule (**a**), vs. a non-planar enantiomer of the 3-isopropyl derivative (**b**), would be shortsighted. Potentiation of antibacterial activity between the diastereomeric 3-(monosubstituted)isopropyl *N*-acyl 2-azetidinones has been observed; those SAR studies, together with $\beta$-lactamase stabilities and mechanism of action studies, will be discussed in later publications.

Subsequent to our preliminary disclosures[1~3] that uncharged *N*-acyl groups sufficiently activate a 3-alkyl-substituted azetidin-2-one to engender potent antimicrobial activity, FIRESTONE *et al.*[18] reported on related 4-acetoxy-substituted *N*-acyl 3-alkyl 2-azetidinones which acylate and then deactivate the serine protease human leukocyte elastase.

## Experimental

### Disk Diffusion Assay

Standardized cell suspensions (inocula) were prepared and stored frozen in the vapor phase of a liquid nitrogen freezer, then thawed at room temperature on the day of assay. An agar medium which best supported the growth of each test organism was prepared and sterilized. The media employed were as

follows: Nutrient agar for *S. aureus* UC 3665; Schaedler agar for *B. fragilis* UC 6513; brain heart infusion agar for *C. perfringens* UC 6509; Mueller-Hinton agar for *S. aureus* UC 6685 and *S. epidermidis* UC 719; and Mueller-Hinton agar supplemented with 5% defibrinated sheeps's blood for *Streptococcus pneumoniae* UC 9207. The agar was cooled to 45~50°C prior to being inoculated with the microorganism. The cooled, inoculated medium was poured into a Nunc Bioassay dish (248 mm × 248 mm, 100 ml per dish), and allowed to solidify at room temperature. Drug-impregnated paper disks were then placed on the surface of the agar medium with a forceps. The dishes were incubated for 20 hours at 35°C. The anaerobic organisms were incubated in a Coy Anaerobic glovebox with an atmosphere of 85% nitrogen, 10% hydrogen, and 5% carbon dioxide. After incubation, the size of the zone of inhibition was read to the nearest millimeter and recorded.

*In Vitro* MIC Assay

The minimum inhibitory concentration (MIC) values for aerobic and anaerobic bacteria were determined by methods previously described.[20] Clindamycin hydrochloride was provided by The Upjohn Company, Kalamazoo, MI; cefoxitin sodium was purchased from the Sigma Chemical Company, St. Louis, MO; aztreonam (Azactam, Squibb Lot AZ039) was obtained from E. R. Squibb & Sons, Princeton, NJ.

IR spectra were determined on either a Perkin-Elmer Infracord or 298 Spectrophotomer, or determined by the Physical and Analytical Chemistry Laboratory, The Upjohn Company. $^1$H NMR were determined on either a Varian EM 390 (90 MHz), or a Bruker AM 300 (300 MHz) spectrometer. Chemical shifts are reported in $\delta$ units, downfield from TMS. Low resolution electron impact (EI) mass spectra were obtained on a CEC-21-110B or a Finnigan MAT 8230B or a Finnigan (Varian) MAT CH-7A mass spectrometer at 70 eV using the direct probe. High resolution measurements were obtained on either the CEC-21-110B or MAT 8230B instruments *via* the peak matching technique. Low resolution chemical ionization spectra were obtained on the MAT CH-7A using ammonia, isobutane, or methane as CI gas. FAB mass spectra of compounds were obtained on a Finnigan (Varian) MAT CH5-DF instrument modified for fast atom bombardment (FAB) ionization. The instrument was set up with xenon or argon as the bombarding gas at 8 kV. The data were acquired and analyzed using the UPACS-II data system. Each compound was run using glycerol-thioglycerol (3:1) or 2-hydroxyethyldisulfide (2-HED) as the matrix. In an attempt to confirm the empirical formulas of the compounds, the exact masses of $(M+H)^+$ ions were measured, *via* the peak matching technique. The ions were measured against known cluster adducts of the glycerol-thioglycerol or 2-HED matrix, or ions of polypropyleneglycol added as a reference material. TLC analysis was carried out on glass plates coated with silica gel G (Analtech). Preparative TLC was carried out on 1,000 $\mu$m or 2,000 $\mu$m thick silica gel 20 cm × 20 cm plates (Analtech). Column chromatography was carried out using Silica gel 60 (40~63 $\mu$m, E. Merck, Darmstadt), typically on a 5.0 cm × 0.5 cm column. Visualization of TLC plates was with *p*-anisaldehyde staining or UV light.

For the isopropylidenyl analogs **2a**~**18a**, the spectral data is tabulated in Tables 3 and 4; similarly, the data for the isopropyl compounds is found in Tables 4 and 5. The parent 3-isopropylidene 2-azetidinone (**1**) was prepared as previously described;[10] additional unpublished physical data is given below and in Table 3.

3-(1-Methylethylidene)-2-oxo-1-azetidine (**1**) (U-71117)[10]

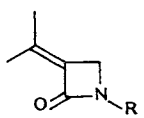
MP 156~158°C.

*Anal* Calcd for $C_6H_9NO$: C 64.84, H 8.16, N 12.60.
Found: C 64.86, H 8.18, N 12.67.

*N*-Acyl-3-isopropylidene Azetidin-2-ones (**2a**~**5a**)

General Procedure A) Anhydride: **3a** (U-70906): A mixture of 0.024 g (0.217 mmol) of **1**, 0.032 g (0.26 mmol) of 4-*N*,*N*-dimethylaminopyridine, and 0.049 ml (0.25 mmol) of valeric anhydride in 0.5 ml of pyridine was stirred at 20°C for 3 hours. The volatiles were removed *in vacuo*, and the residue purified by preparative TLC (1,000 $\mu$m silica gel, EtOAc-hexane (Hex), 1:1 to give 0.28 g (64%) of **3a** as a colorless oil.

Table 3. Physical data of isopropylidene analogs **a**.

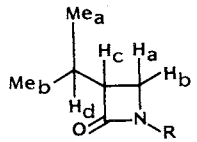


| Compound | $^1$H NMR ($CDCl_3$, 300 MHz) | | | | IR $\nu_{max}$ ($CHCl_3$) | MS | TLC Rf |
|---|---|---|---|---|---|---|---|
| | 4-$CH_2$[a] | *Z*-Me[a] | *E*-Me[a] | N-1 Substituents | $\beta$-Lactam CO, $cm^{-1}$ | (calcd) | EtOAc-Hex (1:1) |
| **1** (U-71117) | 3.70 | 2.06 | 1.73 | 6.67 (1H, br s, NH) | 1739 | 111.0680 (111.0684) | 0.23 |
| **2a** (U-70963)[b] | 3.97 | 2.14 | 1.74 | 2.40 (3H, s, COMe) | 1775 | 153.0785 (153.0790) | 0.47 |
| **3a** (U-70276)[b] | 3.94 | 2.13 | 1.82 | 2.69 (2H, t, $J$=7.5 Hz, $COCH_2$), 1.63 (2H, m), 0.96 (3H, t, $J$=7.5 Hz, Me) | 1770 | 181.1106 (181.1103) | 0.56 |
| **4a** (U-70906) | 3.98 | 2.14 | 1.82 | 2.73 (2H, t, $J$=7.6 Hz, $COCH_2$), 1.66 (2H, m), 1.39 (2H, m), 0.93 (3H, t, $J$=7.3 Hz, Me) | 1769 | 195.1261 (195.1259) | 0.60 |
| **5a** (U-70584) | 3.94 | 2.13 | 1.85 | 2.71 (2H, t, $J$=7.5 Hz, $COCH_2$), 1.68 (2H, m), 1.31 (4H, m), 0.90 (3H, t, $J$=7.5 Hz, Me) | 1768 | — | 0.64 |
| **6a** (U-70965) | 3.96 | 2.12 | 1.80 | 2.70 (2H, t, $J$=7.5 Hz, $COCH_2$), 1.62 (2H, m), 1.30 (6H, br s), 0.83 (3H, t, $J$=7 Hz, Me) | 1768 | 237.1721 (237.1729) | 0.61 |
| **7a** (U-70970) | 4.00 | 2.18 | 1.87 | 5.92 (1H, m, vinyl), 5.04 (1H, d, vinyl), 4.89 (1H, s), 2.77 (2H, t, $J$=7 Hz, $COCH_2$), 2.4 (2H, m), 2.1 (2H, m), 1.3 (10H, br s) | 1767 | — | 0.58 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **9a** (U-80763) | 4.02 | 2.12 | 1.81 | 4.30 (2H, q, $J$=7.1 Hz, $OCH_2$), 1.35 (3H, t, $J$=7.1 Hz, Me) | 1790 | 184.0968 (FAB) (184.0974) | 0.61 |
| **10a** (U-80765) | 4.02 | 2.12 | 1.81 | 4.19 (2H, t, $J$=6.8 Hz, $OCH_2$), 1.73 (2H, m), 0.98 (3H, t, $J$=7.4, Me) | 1790 | 198.1124 (FAB) (198.1130) | 0.65 |
| **11a** (U-71043) | 4.01 | 2.12 | 1.80 | 4.24 (2H, t, $J$=6.7 Hz, $OCH_2$), 1.70 (2H, m), 1.42 (2H, m), 0.95 (3H, t, $J$=7.4 Hz, Me) | 1794 | 212.1302 (FAB) (212.1287) | 0.67 |
| **12a** (U-80219) | 4.04 | 2.12 | 1.80 | 4.38 (2H, m, $OCH_2$), 3.67 (2H, m, $CH_2O$) | 1800 | 213.1004 (213.1001) | 0.37 |
| **13a** (U-80443) | 4.02 | 2.14 | 1.84 | 4.48 (2H, s, $COCH_2O$), 3.65 (2H, q, $J$=7.0 Hz, $CH_2Me$), 1.28 (3H, t, $J$=7.0 Hz) | 1770 | 215 ($M^+ + NH_4$, CI) 168 ($M^+ - C_2H_5$, EI) | 0.52 |
| **14a** (U-80761) | 3.98 | 2.14 | 1.83 | 3.44 (2H, t, $J$=6.2 Hz, $CH_2O$), 3.32 (3H, s, OMe), 2.81 (2H, t, $J$=7.3 Hz, $COCH_2$), 1.96 (2H, m) | 1765 | 212.1293 (FAB) (212.1287) | 0.50 |
| **15a** (U-80470) | 3.95 | 2.13 | 1.81 | 7.2 (5H, m, Ph), 4.49 (2H, s, $OCH_2Ph$), 3.50 (2H, t, $J$=6.1 Hz, $CH_2O$), 2.76 (2H, t, $J$=7.2 Hz, $COCH_2$), 1.74 (4H, m) | 1765 | 301.1678 (301.1678) | 0.76[c] |
| **17a** (U-80462) | 3.98 | 2.14 | 1.83 | 2.99 (2H, dd, $J$=6.7 Hz, $J'$=5.8 Hz), 2.81 (2H, dd, $J$=6.7 Hz, $J'$=4.7 Hz), 2.21 (3H, s, COMe) | 1770 | 209.1043 (209.1052) | 0.44 |
| **18a** (U-80471) | 3.98 | 2.14 | 1.83 | 3.67 (3H, s, OMe), 2.75 (2H, t, $J$=7.0 Hz, $COCH_2$), 2.35 (2H, t, $J$=7.5 Hz, $CH_2CO_2$), 1.70 (4H, m) | 1765 | 253.1321 (253.1314) | 0.70[c] |

[a] Singlet, 2H.
[b] $^1H$ NMR at 90 MHz.
[c] 70% EtOAc - Hex.

Table 4. Physical data of isopropyl analogs **b**.

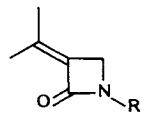



| Compound | $^1$H NMR ($CDCl_3$, 300 MHz) | | | | | | | IR $\nu_{max}$ ($CHCl_3$) $\beta$-Lactam CO $cm^{-1}$ | MS (calcd) |
|---|---|---|---|---|---|---|---|---|---|
| | $H_a$ (dd) ($J_{ab}$, $J_{ac}$)[a] | $H_b$ (dd) ($J_{ba}$, $J_{bc}$) | $H_c$ (ddd) ($J_{cd}$, $J_{ca}$, $J_{cb}$) | $H_d$ | $Me_a$ (3H, d, $J$) | $Me_b$ (3H, d, $J$) | *N*-Substituent | | |
| **2b** (U-70964)[d] | 3.60 (7.5, 7.5) | 3.29 (8, 3) | 3.03 (m) | 2.03 (m) | 1.1 (7) | 1.0 (7) | 2.37 (3H, s, Me) | — | — |
| **3b** (U-70277)[b] | 3.61 (7.8, 6.5) | 3.31 (7.7, 3.6) | 3.05 (8.3, 6.6, 3.7) | 2.02 (m) | 1.09 (6.7) | 1.00 (6.7) | 2.68 (2H, t, $J$=7.5, $COCH_2$), 1.77 (2H, m), 0.98 (3H, t, $J$=7.5 Hz, Me) | 1782 | 183.1259 (183.1252) |
| **4b** (U-70905)[d] | 3.57 (7, 7) | 3.28 (8, 3) | 3.01 (m) | 2.02 (m) | 1.1 (7) | 1.0 (7) | 2.67 (2H, t, $J$=7 Hz, $COCH_2$), 1.52 (4H, m), 0.9 (3H, t, $J$=7 Hz, Me) | 1781 | — |
| **5b** (U-70585) | 3.60 (7.5, 7.5) | 3.28 (7.5, 4) | 3.05 (m) | 2.02 (m) | 1.09 (6) | 1.00 (6) | 2.68 (2H, t, $J$=7.5 Hz, $COCH_2$), 1.64 (2H, m), 1.33 (4H, m) | 1781 | 211.1569 (211.1572) |
| **6b** (U-70966)[d] | 3.55 (7, 7) | 3.26 (7.5, 3) | 3.00 (m) | 1.99 (m) | 1.1 unresol.[c] | 1.0 unresol. | 2.64 (2H, t, $J$=7.5 Hz, $COCH_2$), 1.6 (2H, m), 1.27 (8H, br s), 0.89 (3H, t, $J$=7Hz, Me) | 1782 | 239.1861 (239.1885) |
| **8b** (U-71039) | 3.61 (7.7, 6.5) | 3.30 (7.7, 3.6) | 3.04 (m) | 2.05 (m) | 1.09 (6.7) | 1.0 (6.7) | 2.69 (2H, t, $J$=7.5 Hz, $COCH_2$), 1.65 (2H, t, $J$=7.5 Hz), 1.25 (14H, br s), 0.88 (3H, t, $J$=6.9 Hz, Me) | 1780 | — |
| **9b** (U-80764) | 3.65 (t, 6.8) | 3.35 (7.0, 3.5) | 3.05 (m) | 2.05 (m) | 1.09 (6.7) | 0.99 (6.7) | 4.29 (2H, q, $J$=7.0 Hz), 1.35 (3H, t, $J$=7.2 Hz) | 1800 | — |
| **10b** (U-80766) | 3.66 (t, 6.6) | 3.36 (7.0, 3.5) | 3.05 (m) | 2.03 (m) | 1.09 (6.7) | 1.00 (6.7) | 4.19 (2H, t, $J$=6.7 Hz, $OCH_2$), 1.73 (2H, m, $CH_2$), 0.98 (3H, t, $J$=7.4 Hz, Me) | — | 200.1290 (FAB) (200.1287) |

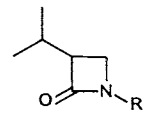
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **11b** (U-71088) | 3.65 (t, 6.5) | 3.35 (6.9, 3.5) | 3.05 (m) | 2.05 (m) | 1.09 (6.7) | 0.99 (6.7) | 4.23 (2H, t, $J$=6.7 Hz, $OCH_2$), 1.69 (2H, m), 1.41 (2H, m), 0.95 (3H, t, $J$=7.4 Hz, Me) | 1802 | 214.1438 (FAB) (214.1443) |
| **12b** (U-80220) | 3.65 (m) | 3.37 (m) | 3.06 (m) | 2.02 (m) | 1.08 (6.7) | 0.99 (6.7) | 4.37 (2H, dd, $J$=5.8 Hz, $J'$=3.8 Hz), 3.65 (2H, m), 3.40 (3H, s) | 1810 | (No $M^+$ observed) |
| **13b** (U-80460) | 3.65 (m) | 3.35 (7.7, 3.7) | 3.08 (m) | 2.03 (m) | 1.09 (6.7) | 1.00 (6.7) | 4.43 (2H, s, $CH_2O$), 3.65 (2H, m), 1.27 (3H, t, $J$=7.0 Hz, Me) | 1785 | 200 $(M+H)^+$ (CI) |
| **14b** (U-80762) | 3.61 (t, 6.7) | 3.30 (m) | 3.05 (m) | 1.98 (m) | 1.09 (6.7) | 0.99 (6.7) | 3.43 (2H, t, $J$=6.3 Hz, $CH_2O$), 3.30 (3H, OMe), 2.78 (2H, m, $COCH_2$), 1.98 (2H, m) | 1780 | 214.1438 (FAB) (214.1443) |
| **15b** (U-80468) | 3.59 (7.5, 6.6) | 3.29 (7.8, 3.6) | 3.02 (8.1, 6.3, 3.6) | 2.02 (m) | 1.08 (6.6) | 0.99 (6.6) | 7.33 (5H, m, Ph), 4.49 (2H, s), 3.49 (2H, t, $J$=6.3 Hz, $CH_2O$), 2.73 (2H, t, $J$=7.2 Hz, $COCH_2$), 1.72 (4H, m) | 1780 | 303.1829 (303.1834) |
| **16b** (U-80719) | 3.62 (7.8, 6.6) | 3.31 (7.8, 3.6) | 3.06 (8.1, 6.6, 3.6) | 2.03 (m) | 1.09 (6.6) | 1.00 (6.6) | 3.65 (2H, t, $J$=6.3 Hz, $CH_2O$), 2.73 (2H, t, $J$=7.3 Hz, $COCH_2$), 2.44 (1H, t, $J$=7.0 Hz, OH), 1.75 (2H, m), 1.62 (2H, m) | 1780 | 214.1444 (FAB) (214.1443) |
| **17b** (U-80461) | 3.62 (7.6, 6.6) | 3.31 (7.7, 3.7) | 3.07 (8.3, 6.6, 3.7) | 2.04 (m) | 1.09 (6.7) | 1.00 (6.7) | 2.95 (2H, t, $J$=6 Hz), 2.78 (2H, m), 2.20 (3H, s, Me) | 1785 | 212 $(M+H)^+$ (CI) |
| **18b** (U-80469) | 3.62 (7.8, 6.6) | 3.30 (7.8, 3.6) | 3.06 (8.1, 6.4, 3.6) | 2.05 (m) | 1.09 (6.7) | 1.00 (6.7) | 3.66 (3H, s, Me), 2.71 (2H, m), 2.35 (2H, m), 1.69 (4H, m) | 1780 | 255.1468 (255.1470) |

[a] $J$ values in Hz.
[b] $^1H$ NMR at 200 MHz.
[c] Unresol; unresolved due to overlap.
[d] 90 MHz.

Table 5. $^{13}C$ NMR data (75.47 MHz, $CDCl_3$).



Isopropylidenes (**a**)



Isopropyls (**b**)

| Position assignment | Chemical shift ($\delta$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **4a** | **9a** | **10a** | **15a** | **18a** | **5b** | **11b** | **15b** | **16b** | **18b** |
| Lactam CO | 171.8 | 159.1 | 159.0 | 171.2 | 170.8 | 171.2 | 166.8 | 171.1 | 171.1 | 170.8 |
| N-CO | 160.1 | — | — | 160.1 | 159.8 | 167.3 | — | 167.5 | 167.4 | 167.3 |
| $N\text{-}CO_2$ | — | 150.3 | 150.2 | — | — | — | 149.7 | — | — | — |
| C=C | 145.4 | 144.3 | 144.2 | 146.5 | 145.3 | — | — | — | — | — |
| C=C (C-3, **a**) | 128.3 | 128.8 | 128.8 | 128.3[b] | 128.3 | — | — | — | — | — |
| $N\text{-}CO_2C$* | — | 62.5 | 67.8 | — | — | — | 66.5 | — | — | — |
| C-4 | 44.9 | 46.0 | 45.9 | 44.7 | 44.6 | 55.1 | 56.2 | 55.3 | 55.1 | 55.4 |
| C-3 (**b**) | — | — | — | — | — | 40.5 | 42.1 | 40.7 | 40.5 | 40.1 |
| N-COC* | 36.2 | — | — | 35.8 | 35.7 | 36.3 | — | 36.2 | 35.8 | 36.1 |
| Me | 21.6 | 21.5 | 21.5 | 21.4[a] | 21.3 | 19.7[c] | 19.8[d] | 20.0[e] | 19.9[f] | 20.0 |
| Me | 20.6 | 20.6 | 20.5 | 20.5[a] | 20.3 | 19.5[c] | 19.0[d] | 19.7 | 19.7[f] | 19.7 |
| Me (chain) | 13.8 | 14.4 | 10.1 | — | 51.2 | 13.6 | 13.7 | — | — | 51.9 |
| Other signals | 26.6 | | 22.0 | 138.3 | 33.4 | 31.0 | 30.7 | 128.5 | 61.6 | 173.7 |
| | 22.3 | | | 128.1[b] | 24.1 | 28.0 | 28.2 | 128.3 | 31.6 | 33.6 |
| | | | | 127.4[b] | 23.5 | 23.6[c] | 20.0[d] | 127.6 | 27.9 | 28.2 |
| | | | | 127.0[b] | | 22.1[c] | | 127.4 | 19.5[f] | 24.3 |
| | | | | 72.5 | | | | 72.8 | | 23.5 |
| | | | | 69.5 | | | | 69.8 | | |
| | | | | 29.0 | | | | 29.1 | | |
| | | | | 21.0[a] | | | | 28.2 | | |
| | | | | | | | | 20.9[e] | | |

[a~f] Values having identical superscripts within a column may be interchanged.

*N*-Acyl 3-Isopropylidene Azetidin-2-ones (**6a ~ 7a**)

General Procedure B) Acid Chloride: **6a** (U-70965): To a solution of 0.025 g (0.23 mmol) of **1** in 5 ml of methylene chloride at 0°C under argon was added 0.041 ml (0.29 mmol) of triethylamine, then over 1 minute, 0.051 ml (0.30 mmol) of octanoyl chloride. The mixture was allowed to stir at 20°C for 1.3 hours, then additional amounts (as above) each of triethylamine and octanoyl chloride were added, and again after an additional 2 hours. The mixture was stirred for 22 hours, then concentrated *in vacuo*. The residue was purified by preparative TLC (conditions as for **3a**) to give 0.38 g (71%) of **6a** as an oil.

*N*-Acyl 3-Isopropylidene Azetidin-2-ones (**13a ~ 18a**)

General Procedure C) Dicyclohexylcarbodiimide Coupling: **13a** (U-80443): To a mixture of 0.020 g (0.18 mmol) of **1**, 0.035 g (0.29 mmol) of *N*,*N*-dimethylamino pyridine, and 0.055 g (0.53 mmol) of ethoxyacetic acid in 1.0 ml of dichloromethane at 20°C under argon was added 0.131 g (0.64 mmol) of dicyclohexylcarbodiimide, and the mixture stirred for 4 hours. The mixture was filtered and the solid was washed with dichloromethane, and the combined filtrates were concentrated *in vacuo*. The residue was purified by preparative TLC (1,000 $\mu$m silica gel, EtOAc - Hex, 30 : 70, 3 elutions) to give 0.027 g (76%) of **13a** as a white solid, mp 63 ~ 65°C.

*N*-Carboxylic Acid 3-Isopropylidene Azetidin-2-one Esters (**9a ~ 12a**)

General Procedure: **10a** (U-80765). To a solution of 0.032 g (0.29 mmol) of **1** and 0.052 g (0.43 mmol) of *N*,*N*-dimethylaminopyridine in 2.5 ml of triethylamine - methylene chloride, 80 : 20 at 0°C was added 72 $\mu$l (0.64 mmol) of *n*-propyl chloroformate dropwise over 1 minute. After 7 hours, an additional 72 $\mu$l

*n*-propyl chloroformate was added, and after an additional 22 hours, the mixture was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by preparative TLC (conditions as for **3a**) to give 0.030 g (53%) of **10a** as a solid, mp 40~42°C.

*N*-Acyl 3-Isopropyl Azetidin-2-ones (**2b**~**18b**)

General Procedure: A mixture of the isopropylidene (25 mg) and 15 mg of 10% palladium/carbon or palladium black in 5 ml of ethyl acetate is alternately evacuated and filled with hydrogen gas from a balloon four times. The mixture is then stirred at 20°C for 2~24 hours, until the absence of starting material is indicated by TLC. The mixture is then filtered through a short plug of diatomaceous earth, the pad washed with 1 ml of ethyl acetate, and the filtrate concentrated *in vacuo*. The isopropyl *N*-acyl azetidinone was isolated as a colorless oil, and being homogeneous by TLC and $^1$H NMR, did not require subsequent purification (purity was deemed >90%). Compound **5b** was purified by filtering through a short Silica gel 60 (40~63 $\mu$m) plug, eluting with Hex, to give an analytically pure sample.

**16b** (U-80719)

The above general procedure using 10% palladium/carbon was followed except 0.2 ml of a solution of 3 drops glacial acetic acid in 1 ml EtOAc was added, and the residue after workup was purified by column chromatography 15:85, then 100:0 EtOAc-Hex to give **16b** as a colorless oil (78%).

3-(1-Methylethyl)-1-(1-oxohexyl)-2-azetidinone (**5b**) (U-70585)

*Anal* Calcd for $C_{12}H_{21}O_2N$: C 68.21, H 10.02, N 6.63.
Found: C 68.00, H 10.15, N 6.57.

3-(1-Methylethylidene)-2-oxo-1-azetidinecarboxylic Acid, Propyl Ester (**10a**) (U-80765)

*Anal* Calcd for $C_{10}H_{15}O_3N$: C 60.90, H 7.67, N 7.10.
Found: C 60.43, H 7.24, N 6.90.

3-(1-Methylethylidene)-2-oxo-1-azetidinecarboxylic Acid, 2-Methoxyethyl Ester (**12a**) (U-80219)

*Anal* Calcd for $C_{10}H_{15}O_4N$: C 56.33, H 7.09, N 6.57.
Found: C 56.43, H 7.04, N 6.54.

3-(1-Methylethyl)-1-(5-hydroxy-1-oxopentyl)-2-azetidinone (**16b**) (U-80719)

*Anal* Calcd for $C_{11}H_{19}O_3N$: C 61.95, H 8.98, N 6.57.
Found: C 62.22, H 9.38, N 6.63.

3-(1-Methylethyl)-ε,2-dioxo-1-azetidinehexanoic Acid, Methyl Ester (**18b**) (U-80469)

*Anal* Calcd for $C_{13}H_{21}O_4N$: C 61.16, H 8.29, N 5.49.
Found: C 60.98, H 8.49, N 5.04.

Acknowledgments

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