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NUCLEAR ANALOGS OF β-LACTAM ANTIBIOTICS. III. DERIVATIVES INCORPORATING A HYDRAZINE MOIETY.[1]

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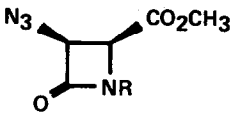
β-lactam antibiotics today play a key role in bacterial chemotherapy. Because of their high potency, wide spectrum of activity, and low mammalian toxicity, they constitute almost ideal agents for the treatment of bacterial infection. Furthermore, they are quite interesting from a chemical point of view. Concentrating a high degree of functionality in a rather small molecular volume, they present a significant challenge to the synthetic organic chemist. By and large, most of the work to date on the β-lactam antibiotics has dealt with structural modifications of naturally derived penicillins and cephalosporins. Recently, however, an increasing number of research groups have turned their attention to total synthesis efforts,[2] which offer the potential of producing novel ring systems with improved biological properties. In this communication, we report our own results on the synthesis of some bi-and tricyclic β-lactam nuclear analogs (7-10) that incorporate a hydrazine moiety.

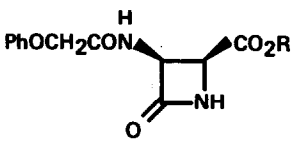
Addition of trifluoroacetic anhydride (1.5 eq.) to a methylene chloride solution of azidoacetic acid (1.5 eq.), triethylamine (3.0 eq.), and the imine derived from 2,4-dimethoxybenzylamine (1.0 eq.) and methyl glyoxalate (1.2 eq.) afforded, in 45% yield,[3] the cis-β-lactam 1.[1a] This method of preparation of 1 is noteworthy in avoiding both the use of the hazardous azidoacetyl chloride and the necessity of preforming the mixed anhydride.[1a,4] Oxidative cleavage (buffered $K_2S_2O_8$[5]) of the dimethoxybenzyl group afforded 2[1b], which was transformed into 3[1a] by sequential reduction (H_2/Pd-C, 1 eq. p-TsOH·H_2O, 95% EtOH, 50 psi, 3 hr) and acylation ($PhOCH_2COCl$, Et_3N, 95% EtOH, 0°). While 3 can also be prepared from 1 by reversing the deblocking and reduction-acylation steps[1], the present method allows the introduction of substituted acetamido groups (e.g. 2-thienylacetamido) that are unstable to the oxidative conditions.

Hydrolysis of 3 (K_2CO_3/CH_3OH-H_2O, 25°, 1 hr) afforded the acid 4[6] (85%), mp 143-145° (dec); ir (nujol mull) 5.53, 5.61 (split β-lactam C=O), 5.76 (acid), 6.08 (amide). Cou-



1 R = 2,4-dimethoxybenzyl

2 R = H



3 R=CH_3

4 R=H

RNHNHR'

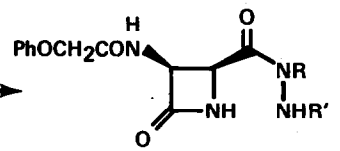
5

a, R+R' = $CH_2CH_2CH_2CH_2$

b, R+R' = $CH_2CH_2CH_2$

c, R+R' = CH_2CH_2CO

d, R=H, R' = CO_2CH_3



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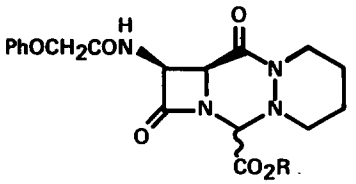

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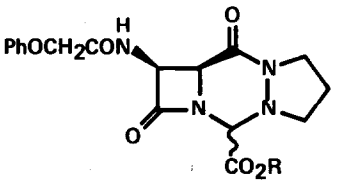

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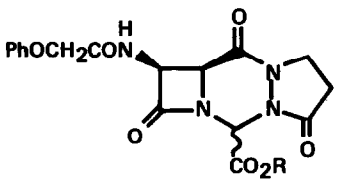

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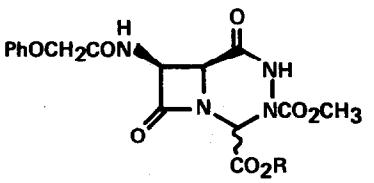

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a, R = CH_2Ph

b, R = H or Na

pling of 4 with hexahydropyridazine (5a)[7] (DCC/THF, 25°, 18 hr) gave 6a in 46% yield, mp 185-187°; ir (nujol mull) 5.58, 5.70 (split β-lactam C=O), 5.93, 6.06 (amides); nmr ($CDCl_3$) δ 5.19 (1H, d, J=5; azetidinone C-4H), 5.52 (1H, dd, J=5,9; azetidinone C-3H). Condensation with freshly distilled benzyl glyoxalate ($BF_3 \cdot Et_2O$/THF, 25°, 18 hr) produced a 32% yield of 7a as a 2:1 mixture of epimers, which were separated by chromatography on silica gel. The major epimer (mp 167-168°) was found to isomerize completely to the minor epimer (mp 146-147.5°) upon treatment with $NaHCO_3$ in aqueous dioxane;[8] 7a (major): ir ($CHCl_3$) 5.60 (β-lactam), 5.71 (ester), 5.91 (amide); nmr ($CDCl_3$) δ 1.6 (4H, m; $-CH_2CH_2-$), 3.1 (4H, m; $>NCH_2-$), 4.19 (1H, d, J=5.5; azetidinone C-4H), 4.50 (2H, s; $PhOCH_2CO-$), 4.81 (1H, s, $>CHCO_2CH_2Ph$), 5.23 (2H, s; $-CO_2CH_2Ph$), 5.53 (1H, dd, J=5.5, 8; azetidinone C-3H), 6.7-7.3 (5H, m; PhO), 7.32 (5H, s; $PhCH_2-$); 7a (minor): ir (nujol mull) 5.60 (β-lactam), 5.73 (ester), 5.94, 6.08 (amides); nmr ($CDCl_3$) δ 1.8 (4H, m; $-CH_2CH_2-$), 2.5-4.0 (4H, m; $>N-CH_2-$), 4.33 (1H, d, J=6; azetidinone C-4H), 4.44 (2H, s; $PhOCH_2CO$), 5.12 (1H, s; $>CHCO_2CH_2$ Ph), 5.21 (2H, s; $-CO_2CH_2Ph$), 5.5 (1H, m; azetidinone C-3H), 6.7-7.2 (5H, m; PhO), 7.32 (5H, s; $PhCH_2-$). Each ester was then hydrogenolyzed (H_2/Pd-C, 1 eq. $NaHCO_3$, dioxane-H_2O, 1 hr) in near quantitative yield to the respective carboxylate salts;[9] 7b (major): ir (nujol mull) 5.67 (β-lactam), 5.95, 6.10 (amides), 6.21 (carboxylate); 7b (minor); ir (nujol mull) 5.68 (β-lactam), 5.95, 6.09 (amides), 6.20 (carboxylate). Both epimers of 7b showed modest activity against Staph. aureus (minimum inhibitory concentrations of 200 μg/ml).

With a view toward enhancing β-lactam reactivity through increased ring strain, 5b[10] was similarly converted to 8b, which exhibited improved activity against Staph. aureus (MIC = 25 μg/ml). In an attempt to obtain derivatives in which the β-lactam carbonyl is activated by electronic factors, hydrazines 5c[11] and 5d were transformed into acids 9b[12] and 10b, respectively.[13] However, neither showed activity against B. subtilis at 500 μg/ml.

The Δ^3 double bond present in naturally derived cephalosporins is believed to be critical for the antibacterial activity of 4,6-systems, since Δ^2-cephalosporins[14] and saturated nuclear analogs[15,16] are devoid of significant activity. In this regard, even the rather limited antibacterial activity of 7b (both carboxylate epimers) and 8b is an unexpected finding.

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References and Notes

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12. Conversion of 6c to 9a with $BF_3 \cdot Et_2O$ catalysis was unsuccessful, stopping at the carbinolamide apparently because of the reduced nucleophilicity of the amide nitrogen. The desired transformation was effected by treatment of the carbinolamide with $SOCl_2$/pyridine.
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