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NUCLEAR ANALOGS OF β-LACTAM ANTIBIOTICS. V. SYNTHESIS OF A BENZO-FUSED CARBOCYCLIC β-LACTAM.[1]

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Because of their central role in the treatment of bacterial infection, the β-lactam antibiotics have received a tremendous amount of attention since their discovery. While the majority of chemical effort has been devoted to the preparation of semi-synthetic penicillins and cephalosporins, recent work has increasingly focused on total synthesis, through which may be obtained novel compounds not readily derived from natural sources.[1,2] One of the significant results from these efforts is the observation that biological activity is retained when the sulfur atom of cephalosporins is replaced by carbon.[2] As part of our continuing work in this area,[1] we decided to synthesize a benzo-fused carbocyclic β-lactam (10), which has among its novel features: (1) four sp^2 centers in the ring fused to the β-lactam; and (2) increased steric bulk, lipophilicity, and electron density at positions 1 and 2 (cephalosporin numbering).

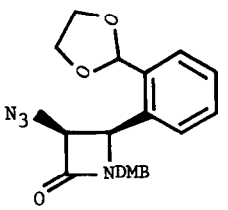
Addition of trifluoroacetic anhydride (34.4 g, 164 mmol) over 1.5 hr. to 940 ml of ice cold methylene chloride containing azidoacetic acid (16.4 g, 162 mmol), triethylamine (36.5 g, 360 mmol), and the imine derived from 2,4-dimethoxybenzyl amine (7.3 g, 43.7 mmol) and phthalaldehyde monoethylene acetal[3] (7.8 g, 43.8 mmol) afforded, in 49% yield, the cis-β-lactam 1,[6] mp 128-129°; ir (nujol mull) 4.71 (azide), 5.70 (β-lactam); nmr ($CDCl_3$) δ 4.75 (1H, d, J=5; azetidinone C-4H), 5.07 (1H, d, J=5; azetidinone C-3H). Oxidative cleavage of the dimethoxybenzyl group with buffered $K_2S_2O_8$[1,7] gave a 49% yield of 2,[8] mp 61-62°, which was converted to 3 by sequential reduction (H_2/Pd-C, EtOAc, 50 psi, 4.5 hr) and acylation ($PhOCH_2COCl$, Et_3N, EtOAc, 0°); 21%, mp 151-152°; ir (nujol mull) 3.10 (N-H), 5.61 (β-lactam), 5.99 (amide), 6.43 (amide

II); nmr ($CDCl_3$-DMSO-d_6) δ 4.02 (4H, s; dioxolane C-4H and C-5H), 4.26 (2H, s; $-OCH_2CO-$), 5.5 (2H, m; azetidinone C-3H and C-4H), 5.84 (1H, s; dioxolane C-2H).

Compound 3 could also be prepared more conveniently and in better yield by an alternate sequence of reactions. Thus, treatment of the aforementioned imine (7.0 g, 21.5 mmol) in 65 ml of ice cold methylene chloride with triethylamine (2.6 g, 25.8 mmol) and phthaloylglycyl chloride (5.5 g, 24.8 mmol; added in 40 ml CH_2Cl_2 over 15 min.) afforded a 64% yield of cis-β-lactam 4, mp 170-172°; ir (nujol mull) 5.70 (β-lactam), 5.63, 5.82 (phthaloyl C=O); nmr ($CDCl_3$) δ 5.26 (1H, d, J=5; azetidinone C-4H), 5.55 (1H, d, J=5; azetidinone C-3H). Removal of the phthaloyl group was effected with methyl hydrazine (1.7 eq., CH_2Cl_2, 25°, 72 hr), and the resulting amine was acylated ($PhOCH_2COCl$, Et_3N, CH_2Cl_2, 0°) to give an 87% overall yield of 5, mp 139-140°; ir (nujol mull) 2.98 (N-H), 5.71 (β-lactam), 5.93 (amide), 6.49 (amide II); nmr ($CDCl_3$) δ 5.16 (1H, d, J=5.5; azetidinone C-4H), 5.52 (1H, dd, J=5.5, 9; azetidinone C-3H). Buffered $K_2S_2O_8$ oxidation then afforded 3 in 67% yield.

Condensation of 3 with freshly distilled benzyl glyoxalate (Et_3N,[9] THF, 25°, 18 hr) gave after chromatography on silica gel an 81% yield of carbinolamide 6 as an epimeric mixture; ir (film) 2.90 (broad, O-H and N-H). Conversion to chloride 7 ($SOCl_2$-pyridine, -6°, 2 hr) and then treatment with triphenylphosphine (2.2 eq. pyridine, THF, 7 hr reflux) produced ylide 8 in 62% yield.[10] Hydrolysis of 8 (aqueous acetone, p-TsOH, 25°, 2.5 hr) afforded directly the cyclized structure 9, no doubt via Wittig reaction of the intermediate aldehyde; 65%, mp 165-166°; ir (KBr) 2.92 (N-H), 5.60 (β-lactam), 5.77 (ester), 5.98 (amide), 6.59 (amide II); nmr ($CDCl_3$) δ 4.52 (2H, s; $-OCH_2CO-$), 5.15 (1H, d, J=5; azetidinone C-4H), 5.33 (2H, s; $-CO_2CH_2Ph$), 6.05 (1H, dd, J=5, 8; azetidinone C-3H), 6.5-7.5 (16H, m; vinyl, aromatic, and N-H); uv (EtOH) λ_{max} 238 (18,800), 330 (12,700). Hydrogenolysis of the benzyl ester (1 atm. H_2/Pd-C, THF) then afforded an 88% yield of acid 10, mp 167-168°; ir (KBr) 2.91 (N-H), 3.5-4.3 (broad, O-H), 5.58 (β-lactam), 5.89 (acid), 5.95 (amide), 6.48 (amide II); nmr ($CDCl_3$-CD_3OD) δ 4.55 (2H, s; $-OCH_2CO-$), 5.17 (1H, d, J=5; azetidinone C-4H), 6.08 (1H, d, J=5; azetidinone C-3H), 6.5-7.5 (10H, m; aromatic and vinyl); uv (EtOH) λ_{max} 234 (22,500), 319 (14,200).

Although active against B. subtilis at 25 μg/ml, 10 proved to be inactive against a spectrum of gram positive and gram negative bacteria at concentrations of 1000 μg/ml. That this inactivity is not due to an unreactive β-lactam carbonyl was demonstrated by pseudo first order kinetics experiments, in which 10 reacted with hydroxylamine (100 fold excess, 25°) ca. 20 times faster than did several desacetoxycephalosporins. It thus seems likely that the lack of



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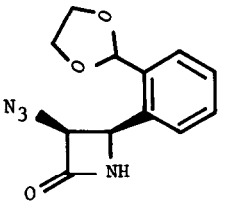

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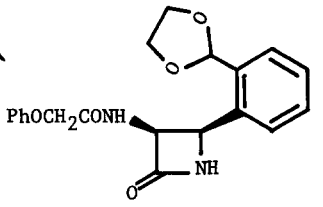

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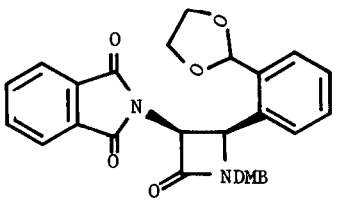

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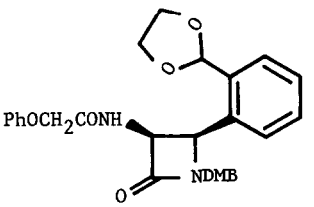

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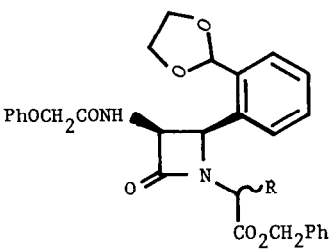
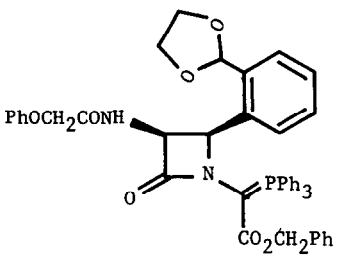


6 R = OH
7 R = Cl



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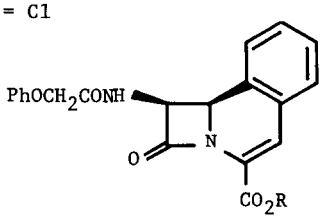

9 R = CH_2Ph
10 R = H

biological activity is due to increased steric bulk, lipophilicity and/or electron density resulting from the fused benzene ring.

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References and Notes

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3. Prepared in 77% yield by oxidation of o-formylbenzyl alcohol, ethylene acetal[4] with buffered pyridinium chlorochromate.[5]
4. C. Brown and M. V. Sargent, J. Chem. Soc. (C), 1818 (1969).
5. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).
6. All new compounds reported herein were characterized spectroscopically. The elemental composition of all β-lactams except 6 and 7 was confirmed by combustion analysis or exact mass measurement.
7. H. L. Needles and R. E. Whitfield, J. Org. Chem., 29, 3632 (1964).
8. This reaction also produced lesser amounts of the corresponding benzaldehyde (through acetal hydrolysis) and the 2-hydroxyethyl benzoate (via oxidation of the dioxolane.)
9. The advantages of triethylamine in this type of reaction were communicated to us by N. Hall and D. Jakas, SK&F Laboratories.
10. For similar transformations in systems closer to the natural cephalosporins, see, inter alia, R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, Helv. Chim. Acta., 55, 408 (1972).