

SYNTHESIS OF A NOVEL β -LACTAM CONTAINING NUCLEUS: 1-CARBOXY-2-AZA-TRICYCLO[4.2.2.0^{2,5}]DECANE-3-ONE.

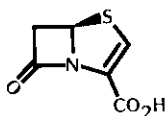
G. Michael Bright, Michael F. Dee and Michael S. Kellogg*.

Pfizer Central Research, Central Research, Pfizer Inc. Groton, Connecticut 06340.

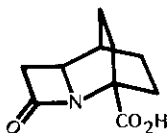
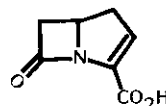
Abstract: The synthesis of 1-carboxy-2-aza-tricyclo[4.2.2.0^{2,5}]decane-3-one 1, a novel β -lactam carboxylate, from bicyclic amide carboxylate 4 via an efficient triplet sensitized photochemical diazo insertion reaction to produce β -lactam 12 has been described.

With the advent of novel β -lactam fermentation products (clavulanic acid¹, thienamycin²) has come the design and synthesis of agents like CP-45,899⁴ and the penem antibacterials⁵. These are novel β -lactam structures of synthetic or semisynthetic origin with excellent medicinal potential showing considerable promise for the treatment of increasingly resistant bacterial infections. Two major features distinguish these compounds structurally from the classical penicillin-cephalosporin antibiotics; the absence of an amido linkage to the β -lactam, and nuclear modifications. Nevertheless, they interact with the same biological enzyme systems (penicillin binding proteins) as the classical β -lactam antibiotics⁶. Only a reactive β -lactam ring connected through nitrogen to a carboxylate remains structurally common to this entire class of bacterial enzyme inhibitors.

We wish here to describe the synthesis of a novel β -lactam containing nucleus possessing these features in a unique structural array. Our target 1 was chosen because of a close isosteric relationship with the cephalosporin, penem, carbapenem group of antibacterials, as judged by comparative examination of molecular models. Furthermore, we expected the tricyclic system to activate the β -lactam through increased ring strain.



Penem

1

Carbapenem

Synthesis of 1 (Scheme I) was initiated by the preparation of known bicyclic amide carboxylate 4⁷. Conversion of 4 sodium salt to crystalline benzyl ester 5 with benzyl bromide in DMF proceeded in 65% yield. Selective reduction of the amide moiety required a two step procedure.⁸

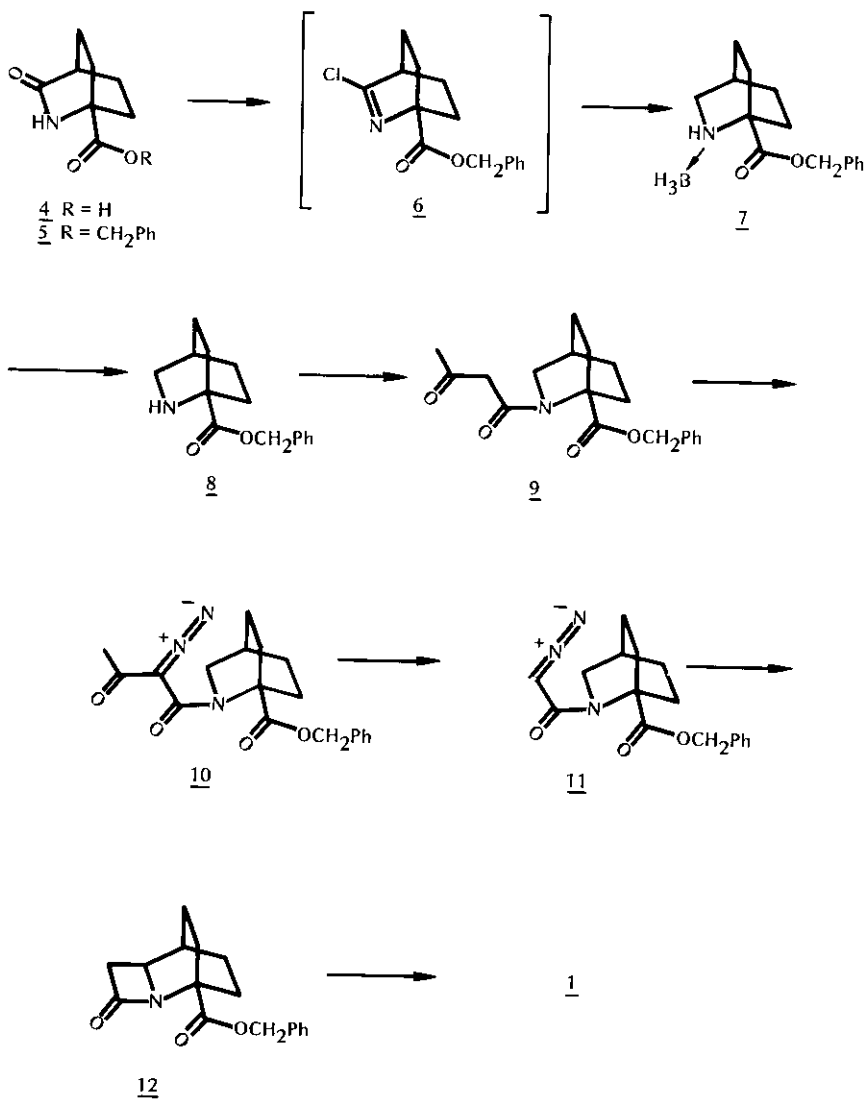
Treatment of 5 with a small excess of phosgene in dichloromethane in the presence of Amberlyst A-21 resin produced imino chloride 6, which was not isolated. After removal of the basic resin, 6 was reduced in dry tetrahydrofuran with excess tetra-n-butyl ammonium borohydride to give, after an aqueous acid-base workup, amine-borane complex 7 (68%) [IR (neat) 3200, 2350, 1730 cm^{-1}]. Amine 8 was liberated from complex 7 by exposure to HCl gas in a chloroform benzyl alcohol solution. The HCl salt (75%, mp 190 $^{\circ}$) was collected after trituration with ether. Extraction from aqueous base gave 8 which was transformed to keto-amide 9 by condensation with diketene in CH_2Cl_2 , the resulting solution was treated in situ with an excess of p-toluenesulfonylazide and triethylamine at reflux in CH_2Cl_2 .⁹ Chromatography of the product mixture after evaporation of solvent gave diazo compound 10 (72%). Diazo amide 11 was obtained by treatment of 10 with the lithium salt of benzyl alcohol (prepared by addition of n-butyl lithium to benzyl alcohol in THF at -30) at -78 $^{\circ}$ and allowing to warm to -50 $^{\circ}$ for 3 hr.¹⁰ After quenching with acetic acid, chromatography on silica gel gave the desired 11 in 51% yield. Photocyclization of 11¹¹ was best accomplished by irradiation in benzene at 350 nm (Rayonet Reactor) in the presence of a 3 fold excess of benzophenone as sensitizer. After 6.5 hr, IR and TLC indicated that 11 had been consumed. Evaporation of solvent and chromatography on silica gel gave the desired β -lactam 12 in 60% yield. [IR (neat) 1760, 1740 cm^{-1} ; 100 MHz NMR (CDCl_3) δ 7.35 (s, 5), 5.19 (s, 2), 3.61 (X, 1H, J_{ax} =2Hz, J_{bx} =5Hz), 3.1 (AB, 2H, J_{ab} =16 Hz, J_{ax} =2Hz, J_{bx} =5Hz, ν_a =2.95, ν_b =3.21), 2.4 (m, 1H), 1.8 (m, 8H); mass spectrum m/e 285.1358 (285.1365 calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_3$)]. We have found the presence of benzophenone in the irradiation mixture to be extremely useful for photochemical formation of β -lactam rings from diazo precursors. Application of triplet sensitization appears to have been little exploited as a technique in such syntheses of β -lactams.¹² Presumably, the lower energy triplet state, while being very effective in hydrogen atom abstraction and ring closure, is much less prone to the other decomposition pathways available to singlet carbenes.

Hydrogenolysis of the benzyl ester 12 with Pd on CaCO_3 in 50% water-THF gave, after evaporation of THF and lyophilization, a 91% yield of the calcium salt of 1. Examination of this product in assays designed to show ability to inhibit β -lactamase enzymes or inhibit bacterial growth in vitro, showed no outstanding activity.

Acknowledgement:

The authors thank Dr. Michael E. Hendrick for helpful discussions and Dr. Gwen Chmurny and Mr. Richard Ware for nmr and mass spectral measurements respectively.

SCHEME 1



REFERENCES AND NOTES

1. T.T. Howarth, A.G. Brown, and T.J. King, Chem. Comm., 1976; 266; A. G. Brown, D. Butterworth, M. Cole, G. Hanscomb, J.D. Hood, C. Reading, and G.N. Rolinson, J. Antibiotics, 1976, 29, 668.
2. G. Albers-Schonberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, R. Walton, L.J. Ruswinkle, R.B. Morin, and B.G. Christensen, J. Am. Chem. Soc., 1978, 100, 6491.
3. J.D. Hood, S.J. Box, and M.S. Verrall, J. Antibiotics, 1979, 32, 295; S.J. Box, J.D. Hood, and S.R. Spear, J. Antibiotics, S.J. Box, J.D. Hood, and S.R. Spear, J. Antibiotics, 1979, 32, 1239; K. Maeda, S. Takahashi, M. Sezaki, K. Iinuma, H. Naganawa, S. Kondo, M. Ohno, and H. Umezawa, J. Antibiotics, 1977, 30, 770; K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, T. Ishikura, and J. Lein, J. Antibiotics, 1978, 31, 480.
4. A.R. English, J.A. Retsema, A.E. Girard, J.E. Lynch, and W.E. Barth, Antimicrob. Ag. Chemother., 1978, 14, 414.
5. M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest, and R.B. Woodward, J. Am. Chem. Soc., 1979, 101, 6296; I Ernest, J. Gosteli, and R.B. Woodward, J. Am. Chem. Soc., 1979, 101, 6301, H.R. Pfaendler, J. Gosteli, and R.B. Woodward, J. Am. Chem. Soc., 1979, 101, 6306; J. Am. Chem. Soc., 1980, 102, 2039; S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, J. Antibiotics, 1980, 33, 107.
6. B.G. Spratt, V. Johamputra, and W. Zimmerman, Antimicrob. Ag. Chemother., 1977, 11, 852; N.A.C. Curtis, D. Orr, G.W. Ross, and M.G. Boulton, Antimicrob. Ag. Chemother., 1979, 16, 533.
7. P.W. Feit and H. Frey, British Patent, 1,115,817 (1968).
8. M.E. Kuehne and P.J. Shannon, J. Org. Chem., 1977, 42, 2082.
9. M. Regitz, Synthesis, 1972, 351.
10. V. Georgian and W.H. Koster, Heterocycles, 1977, 7, 1009; S. Oida, A. Yoshida, and E. Ohki, Chem. Pharm. Bull., 1978, 26, 448.
11. E.J. Corey and A.M. Felix, J. Am. Chem. Soc., 1965, 87, 2518.
12. S.D. Burke and P.A. Grieco, Org. Reactions, 1979, 26, 361; R.J. Ponsford and R. Southgate, Chem. Comm., 1979, 846.

Received, 19th May, 1980