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SYNTHESIS OF NOVEL FUSED β-LACTAMS BY INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS. 3.[1] 6-PHENOXYACETAMIDO-7-OXO-1,3-DIAZABICYCLO[3.2.0]HEPTANE-2-CARBOXYLIC ACIDS

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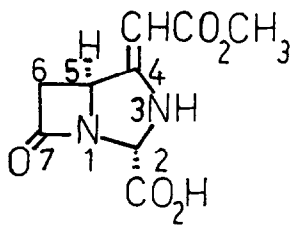
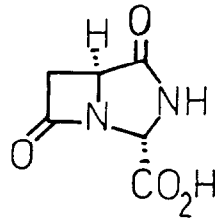
Summary: 4-Methoxycarbonylmethylene-6-phenoxyacetamido-7-oxo-1,3-diazabicyclo[3.2.0]heptane-2-carboxylic acid and 4,7-dioxo-6-phenoxyacetamido-1,3-diazabicyclo[3.2.0]heptane-2-carboxylic acid have been prepared.

A recent communication[2] from these laboratories described the total synthesis of the 7-oxo-1,3-diazabicyclo[3.2.0]heptane ring system. The derivatives (1)[3] and (2) were antibacterially inactive, but it was hoped that the incorporation of a cis acylamino side-chain might activate the β-lactam and improve activity.

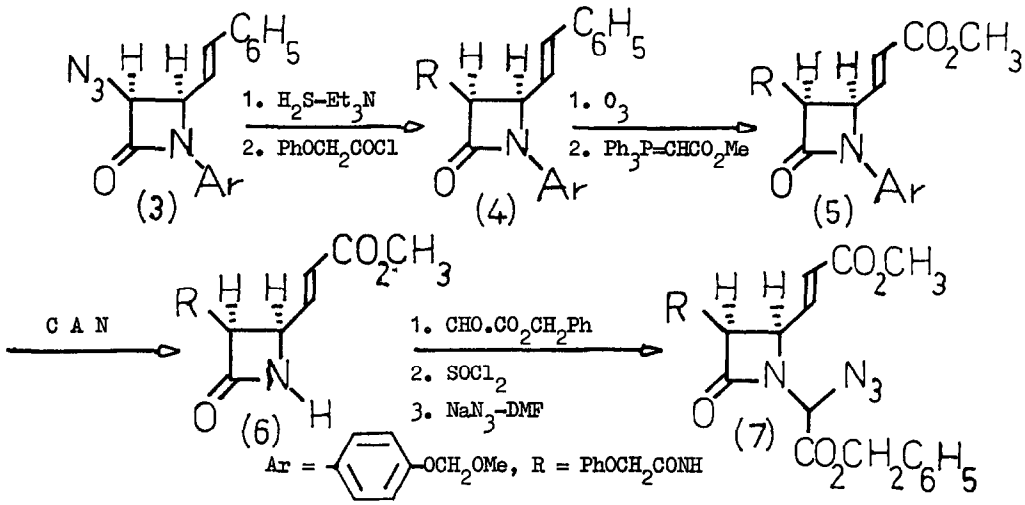


(1)

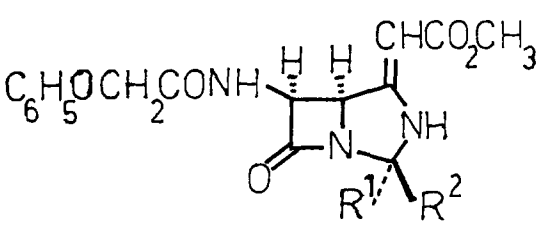


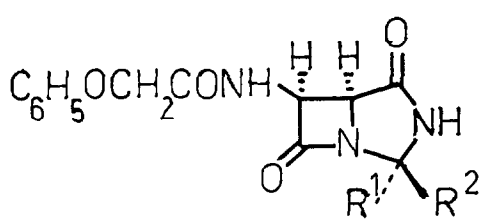
(2)

Addition of the mixed anhydride of azidoacetic acid and trifluoroacetic anhydride[4] to a mixture of triethylamine and the Schiff base from p-methoxymethoxyaniline[5] and cinnamaldehyde afforded the cis β-lactam (3)[6] [85%, m.p. 111 - 112°C] with none of the trans isomer detected. The azide was reduced with hydrogen sulphide-triethylamine[7] and the product acylated with phenoxyacetyl chloride to provide (4) [96%, m.p. 186 - 187°C]. Ozonolysis of (4) [(i) EtOAc, -76°C; (ii) Ph_3P], followed by addition of methoxycarbonylmethylenetriphenylphosphorane, afforded the pure E-isomer (5), after recrystallisation[8] (62%, m.p. 178 - 179°C). Removal of the N-substituent with ceric ammonium nitrate (CAN)[5], then gave the azetidinone (6) [70%, m.p. 147 - 148°C], which was progressed to the azide (7) [2 : 1 mixture of isomers], as previously described.[2]



When (7) was heated in refluxing toluene for 24h (1mg ml^{-1}, under argon), rapid chromatography of the product on silica gel afforded the crystalline enamine (8) (12%), m.p. 131 - 132°C (dec.); $\lambda_{max.}$ (EtOH) 275nm (ε16,600); $\nu_{max.}$ ($CHCl_3$) 3400, 3350, 1807, 1750, 1690sh., 1680 and 1612cm^{-1}; δ ($CDCl_3$) (250MHz) 3.69 (s, OMe), 4.49 and 4.58 (ABq, J 15Hz, $PhOCH_2$), 4.71 (d, J 1Hz, =CH), 4.79 (dd, J 6 and 1Hz, 5-H), 5.20 (s, CO_2CH_2Ph), 5.66 (s, 2-H), 5.83 (dd, J 9 and 6Hz, 6-H), 6.85 - 7.4 (m, aromatics), and 8.23br (s, enamine NH). Further elution of the column gave fractions (39%) containing both (8) and (9), and finally pure (9) (14%) which was isolated as an amorphous solid, $\lambda_{max.}$ (EtOH) 274nm (ε, 17,700); $\nu_{max.}$ ($CHCl_3$) 3400, 3350, 1807, 1758, 1690sh., 1680 and 1630cm^{-1}; δ ($CDCl_3$) (250MHz) 3.78 (s, OMe), 4.49 and 4.57 (ABq, J 15Hz, $PhOCH_2$), 4.65 (d, J 1Hz, =CH), 4.72 (ddd, J 6, 1 and ca. ½Hz, 5-H), 5.13 (d, J ca. ½Hz, 2-H), 5.31 (s, CO_2CH_2Ph), 5.84 (dd, J 9 and 6Hz, 6-H), 6.85 - 7.5 (m, aromatics), and 8.25br (s, enamine NH).





(8) $R^1 = CO_2CH_2Ph$, $R^2 = H$

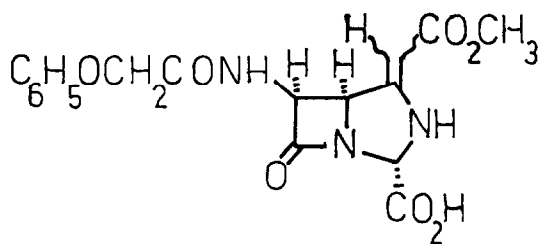
(9) $R^1 = H$, $R^2 = CO_2CH_2Ph$

(10) $R^1 = CO_2CH_2Ph$, $R^2 = H$

(11) $R^1 = CO_2H$, $R^2 = H$

The Z-geometry of the double bond and the stereochemistry at C (2) for each epimer were assigned by analogy with the corresponding unsubstituted derivatives.[2] Treatment of the epimer (9) with the 'unnatural' C (2) stereochemistry with 1,5-diazabicyclo[5.4.0]undec-5-ene caused degradation, no isomerisation to (8) being observed.

Hydrogenation of (8) in dioxan using 10%Pd-C gave the free acid (12). Nmr spectroscopy clearly indicated that partial isomerisation of the enamine double bond had occurred as well as the desired ester cleavage, δ [$(CD_3)_2SO$] (250MHz) (2 : 1 mixture of isomers) *inter alia* 3.42 and 3.59 (2s's, together 3H), 4.41 and 4.94 (s and d, J 1Hz; =CH), 4.7 and 5.01 (d, *J* 5.8Hz and dd, *J* 6.2 and *ca.* 1Hz; 5-H), 5.33 and 5.37 (2s's; 2-H), 5.61 and 5.68 (dd, *J* 8.4 and 5.8Hz and dd *J* 8.4 and 6.2Hz; 6-H). The material was antibacterially inactive.



(12)

Ozonolysis of the enamine (8) (EtOAc, -76°C), followed by reduction of the ozonide (Me_2S) afforded the amide (10), m.p. 158 - 159°C (dec.); $\nu_{max.}$ (Nujol) 3250, 1810, 1750, 1725 and 1650cm^{-1}; δ ($CDCl_3$) (250MHz) 4.12 (dd, *J* 6.3Hz, 5-H), 4.5 (s, $PhOCH_2$), 5.22 (AA' system, CO_2CH_2Ph), 5.35 (dd, *J* 8.2 and 6.3Hz, 6-H), 5.53 (s, 2-H), 6.9 - 7.03 (m, aromatics), 7.25 - 7.4 (m, aromatics), 8.41 (d, *J* 8.2Hz, side-chain NH), and 8.79br (s, ring NH). The acid (11) was also shown to be inactive.

The synthesis of the corresponding aza-cepham derivatives is reported in the succeeding paper.

References and Notes

1. For Part 2 in this series, see M. J. Pearson, J. Chem. Soc., Perkin Trans I, 1981, 3, 2544.

2. C. L. Branch and M. J. Pearson, J. Chem. Soc., Chem. Commun., 1981, 946.

3. All synthetic compounds are racemic mixtures, but only one enantiomer is depicted for convenience.

4. A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, Tetrahedron. Lett., 1973, 2319.

5. T. Fukuyama, R. K. Frank, and C. F. Jewell, Jr., J. Am. Chem. Soc., 1980, 102, 2122.

6. All new compounds were fully characterised spectroscopically and gave correct elemental analyses and/or molecular ion, high resolution mass measurement.

7. T. W. Doyle, B. Belleau, B-Y. Luh, C. F. Ferrari, and M. P. Cunningham, Can. J. Chem., 1977, 55, 468.

8. All recrystallisations were done from ethyl acetate–hexane.

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