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SYNTHESIS OF NOVEL FUSED β-LACTAMS BY INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS.5[1]. TRIAZOLOCEPHEMS AND TRIAZOLOPENAMS

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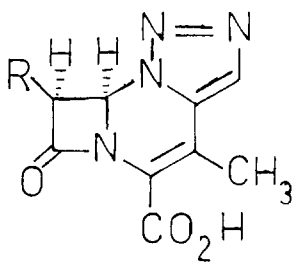
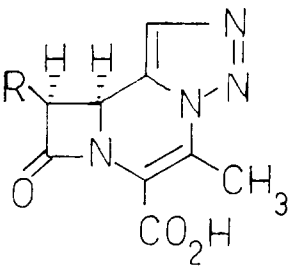
Summary: Tricyclic triazolocephem and triazolopenam carboxylic acids have been synthesised, but only the former exhibited antibacterial activity.

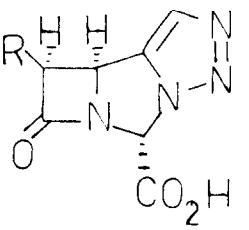
Triazolocephems of type (1) have been shown [2] to possess a level of antibacterial activity that was of sufficient interest for the investigation to be extended to the synthesis of related systems, in the hope of finding more potent derivatives. We now report the preparation of the isomeric system (2)[3] and the triazolopenam (3).



(1)



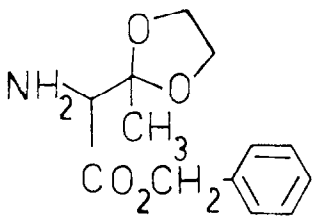
(2)



(3)

R = $PhOCH_2CONH$

Freshly prepared 3-trimethylsilyl-prop-2-ynal[4] was condensed with the amine (4)[5] to afford the Schiff base (5). Compound (5) was then treated with the mixed anhydride from azidoacetic acid and trifluoroacetic anhydride[6], in the presence of triethylamine, to afford the trans β-lactam (6)[7] as a mixture of isomers (*) (4 : 1) (22%), and the two separable cis β-lactams (7) (2 : 1) (22%), the minor component being crystalline, m.p. 70-72°C.



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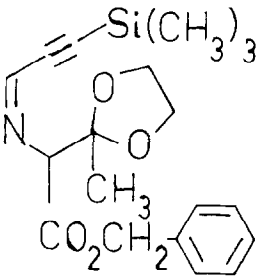

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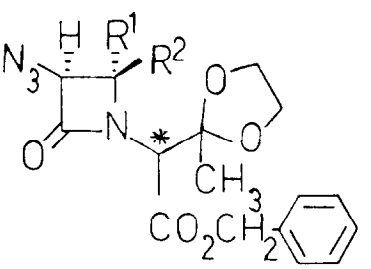
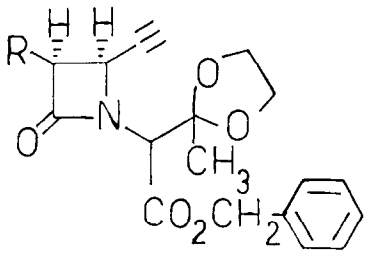


(6) $R^1 = C\equiv C\text{-}Si(CH_3)_3$ $R^2 = H$

(7) $R^1 = H$, $R^2 = C\equiv C\text{-}Si(CH_3)_3$

Removal of the trimethylsilyl group from (7) (Et_4NF, THF), followed by reduction[8] and acylation with phenoxyacetyl chloride provided the ethynyl derivative (8). Hydrolysis[5] of (8) with 95% trifluoroacetic acid gave the enol (9), m.p. 115-116°C, ν_{max} (Nujol) 3345, 3260, 1780, 1755, 1695, and 1620 cm^{-1}; $\delta(CDCl_3)$ 2.16(s, Me), 2.31 (d, J 2Hz, C≡CH), 4.56 (s, $PhOCH_2$), 4.59(dd, J 5 and 2Hz, 4-H), 5.18 (s, CO_2CH_2Ph), 5.38(dd, J 9 and 5Hz, 3-H), 6.8-7.4 (m, aromatics), 12.32(s, exch D_2O, enolic OH).

Conversion of (9) into the mesylate (10) activated the double bond towards nucleophilic attack and allowed the preparation (NaN_3, DMF) of the vinyl azide (11), as a mixture of geometric isomers, ν_{max} 3400(NH), 3300(≡C-H), 2120 (azide), 1785 (β-lactam), 1730 (ester) 1695 (amide), and 1630 (double bond) cm^{-1}.



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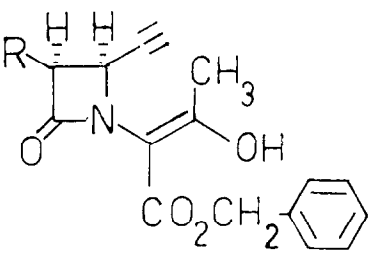

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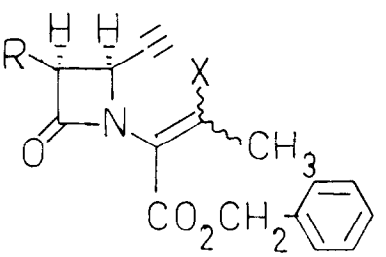
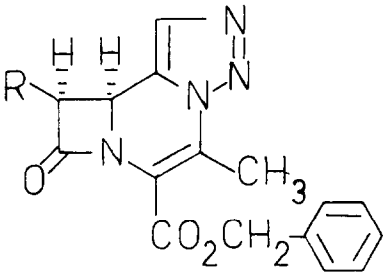


(10) X = OSO_2CH_3

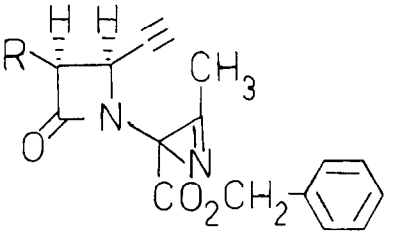
(11) X = N_3

R = $PhOCH_2CONH$

When (11) was heated at reflux in benzene for 15 min, smooth intramolecular cycloaddition occured to give the triazolocephem (12) in 49% yield, λ_{max} (EtOH) 301nm (ε_M 9,500); ν_{max} ($CHCl_3$) 3410(NH), 1790(β-lactam), 1720 (ester), 1690 (amide) and 1630 (double bond) cm^{-1}. The triazole (12) was presumably derived from the Z-isomer (11), thermal decomposition of the minor E-isomer giving the azirine[9] (13) (12%).



(12)

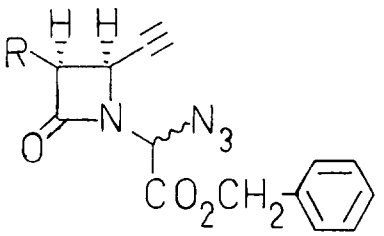


(13)

R = $PhOCH_2CONH$

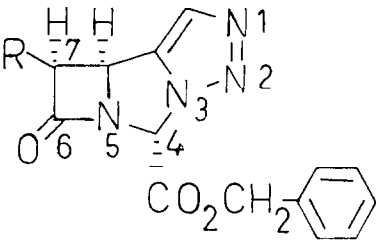
Hydrogenolysis of (12) over 10% Pd-C in aqueous dioxan gave the acid (2) as a white amorphous solid, λ_{max} (EtOH) 288nm (ε_M 6400): ν_{max} (KBr) 3400br, 1760, 1675, and 1630cm^{-1}; $\delta(CD_3OD/D_2O)$ 2.81(s,Me), 5.25(dd, J 5 and ca. 1Hz, β-lactam), 5.67(d, J 5Hz, β-lactam) 6.5-7.5(m, aromatics), and 7.6 (d, J ca. 1Hz, =CH in triazole ring). The material (2) was antibacterially active but the degree of activity was less than that observed in the isomeric series (1)[2].

The azido-acetylene (14) was the key intermediate for the synthesis of the triazolopenam (15).



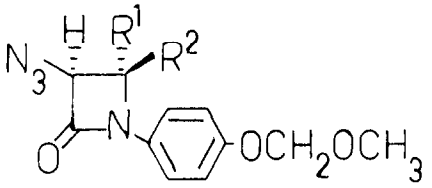
(14)

R = $PhOCH_2CONH$



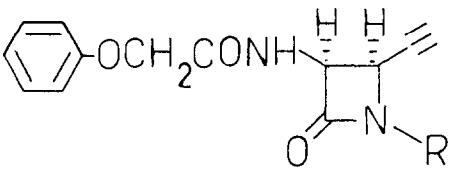
(15)

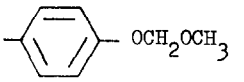
Accordingly the lactam (16) (71%) was prepared via the standard ketene-imine cycloaddition route. Traces of trans isomer (17) (0.25%) were also isolated. Reduction of (16) followed by acylation and treatment with tetraethylammonium fluoride provided the acetylene (18) (90%), which was deblocked ($Ce(NH_4)_2(NO_3)_6$ in aqueous THF)[10] to give the azetidinone (19) (60%), m.p 190-191°C, ν_{max} (Nujol) 3280, 3250, 1768, and 1675 cm^{-1}; $\delta[(CD_3)_2SO]$ 3.45 (d, J 2Hz, ≡CH), 4.48 (dd, J 5 and 2Hz, 4-H), 4.58 (s, $-CH_2CON$), 5.19 (dd, J 9 and 5Hz, 3-H), 6.8-7.4 (5H, aromatics), 8.68(s,exch.D_2O,β-lactam NH), and 8.92 (d, J 9Hz, side-chain NH).



(16) $R^1 = H$, $R^2 = C{\equiv}C\text{-}Si(CH_3)_3$

(17) $R^1 = C{\equiv}C\text{-}Si(CH_3)_3$, $R^2 = H$



(18) R = 

(19) R = H

The azide (14) (1 : 1 mixture of epimers) was then prepared[12] and heated at reflux in toluene for 36h (1 mg ml^{-1}, argon) to afford the triazolopenam (15) (18%) as a single product, m.p. 168-170°C, ν_{max} ($CHCl_3$) 3400 (NH), 1820 (β-lactam), and 1765 cm^{-1}. The absence of coupling between the C-7 (δ5.72) and C-4 (δ6.49) in the ^1H n.m.r. spectrum of (15) indicated that the C-4 proton had the β- configuration[12]. The C-4 proton also showed long range coupling (J 0.9 Hz) to the other β-lactam proton (δ 5.33), which in turn displayed the expected coupling to the C-7 proton (J 5.5 Hz), and allylic coupling (J 0.8 Hz) to the triazole ring proton (obscured by aromatics δ 6.8-7.4). Such selectivity in product formation has been observed previously in related systems, and has been attributed to steric factors[12]. Recovered starting material (14) (30%) was essentially a single azide isomer.

Catalytic hydrogenation of (15) afforded the acid (3), ν_{max} (KBr) 1805, 1745, 1675cm^{-1}. The product was not antibacterially active.

References and Notes

1. For Part 4 in this series, see C.L.Branch and M.J.Pearson, Tetrahedron Lett., 1982,23,3003. 2. M.J.Pearson J.Chem.Soc. Perkin. Trans.1, 1981, 3,2544. 3. All synthetic compounds are racemic mixtures, but only one enantiomer is depicted for convenience. 4. H.Hauptmann and M.Mader, Synthesis, 1978, 307. 5. T.W.Doyle, B.Belleau, B-Y Luh, T.T. Conway, M.Menard, J.L. Douglas, D.T-W Chu, G.Lim, L.R. Morris, P.Rivest, and M.Casey, Can. J. Chem., 1977, 55, 484. 6. A.K. Bose, J.C. Kapur, S.D.Sharma, and M.S.Manhas, Tetrahedron Lett., 1973, 2319. 7. All new compounds were fully characterised spectroscopically and gave correct elemental analyses and/or molecular ion, high resolution mass measurement. 8. T.W. Doyle, B. Belleau, B-Y Luh, C.F.Ferrari, and M.P.Cunningham, Can.J.Chem., 1977, 55, 468. 9. G.Smolinsky, J.Am. Chem. Soc., 1961, 83, 4483. 10. T.Fukuyama, R.K. Frank, and C.F. Jewell, Jr., J.Am. Chem. Soc., 1980, 102, 2122. 11. C.L.Branch and M.J.Pearson, J.Chem. Soc., Chem. Commun. 1981, 946. 12. M.Aratani and M.Hashimoto, J.Am.Chem.Soc., 1980,102,6171.

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