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SYNTHESIS OF NOVEL FUSED β-LACTAMS BY INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS. 4.[1] 7-PHENOXYACETAMIDO-8-OXO-1,3-DIAZABICYCLO [4.2.0] OCTANE-2-CARBOXYLIC ACIDS

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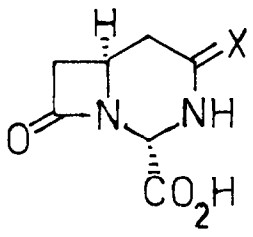
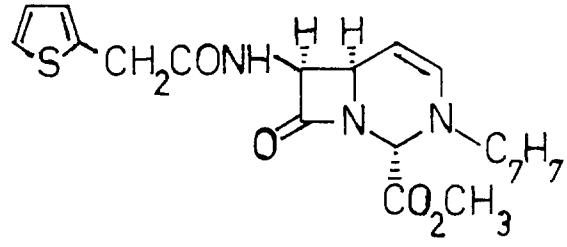
Summary: 6-Phenoxyacetamido-8-oxo-1,3-diazabicyclo [4.2.0] octane-2-carboxylic acids have been synthesised and shown to possess weak antibacterial activity.

We have recently described[2] the synthesis of the 8-oxo-1,3-diazabicyclo [4.2.0] octane ring system. The 7-unsubstituted free acids (1)[3] were antibacterially inactive, but it was surmised that a 7-acylamino group might improve the activity, since the methyl ester (2) has been reported[4] to possess weak antimicrobial activity.

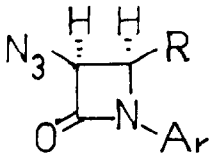


(1) X = $CHCO_2Me$ or O

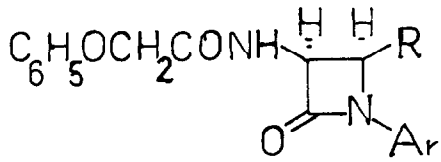


(2)

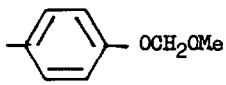
Ozonolysis of the 4-styrylazetidinone (3)[1] provided the aldehyde (4) which was reacted *in situ* with nitromethane (NEt_3, -20°C → RT over 2½h)[5] to give the alcohol (5) (90% overall). Dehydration of (5) ($SOCl_2$, NEt_3) and subsequent reduction ($NaBH_4$, aqueous THF)[6] gave the nitroethylazetidinone (6) (90%). Replacement of azido by phenoxyacetamido[7], and conversion into the nitronate salt (7) (NaOMe; MeOH-MDC), was followed by careful ozonolysis[8] to give (8). The aldehyde (8), was treated with methoxycarbonylmethylenetriphenylphosphorane to yield the olefin (9), as a mixture of isomers (1 : 2, cis : trans, overall yield from (6), 50%).



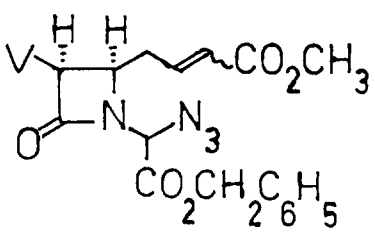
(3) R= CH=CHPh (trans)
(4) R= CHO
(5) R= $CH(OH)CH_2NO_2$
(6) R= $CH_2CH_2NO_2$



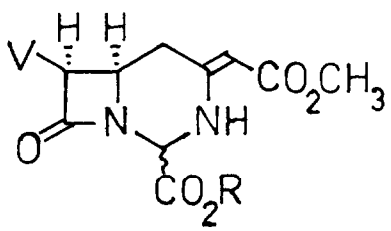
(7) R= $CH_2CH=N^{+}(O^{-})ONa$
(8) R= CH_2CHO
(9) R= $CH_2CH=CHCO_2Me$

Ar =  OCH_2OMe

The azide (10) was then prepared [1] and heated in toluene at 110°C for 4h to give the enamine (11) (72%), as an inseparable mixture of epimers (2 : 1, 2α - H : 2β - H), λ_{max} (EtOH) 276 and 281 nm; ν_{max} ($CHCl_3$) 3410, 3250, 1780 (β-lactam), 1750 (benzyl ester), 1690 (amide), 1670 (methyl ester), and 1615 (enamine) cm^{-1}; δ($CDCl_3$) inter alia 3.54 and 3.55 (each s, CO_2Me), 4.03 (m, 6-H), 4.54 (s, $PhOCH_2$), 4.61 and 4.65 (each s, =CH), 5.11 (dd, J 3.9 and 1.5 Hz, 2α - H), 5.55 (d, J 2Hz, 2β - H), 7.18 (d, J 8Hz amide NH), and 9.15 (s, enamine NH), the additional 1.5Hz coupling shown by the 2α - H is due to the characteristic long range coupling between the α-hydrogens at C(2) and C(7)[9]. The ratio of 2α - H to 2β - H could be altered to an equilibrium value of 2 : 3 by base treatment (DBU), but prolonged contact with base led to degradation.



(10)

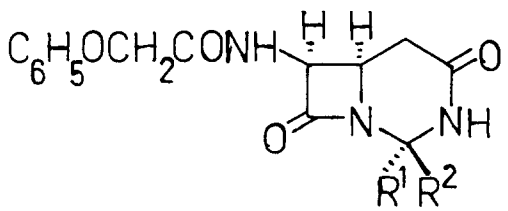


(11) R = CH_2Ph
(12) R = H

V = $PhOCH_2CONH$

Hydrogenation of (11) afforded the corresponding free acid (12), which showed weak antibacterial activity against B.subtilis (MIC = 125 μg/ml) and Streptococcus pneumoniae CN33 (16 μg/ml).

Ozonolysis of the enamine (11), followed by decomposition of the ozonide [P(p-OMePh)$_3$] gave the separable amide epimers (13) m.p. 168–169°C, ν_{max} (Nujol) 3255 (amide NH's), 1785 (β-lactam), 1745 (ester), 1760 (side-chain amide), and 1650 (amide), δ($CDCl_3$) 2.36 and 2.61 (ABq, J 18Hz higher field arm further coupled, d, J 8Hz; lower field arm further coupled, d, J 6Hz, ring CH_2), 4.24 (ddd, J 8, 6, and 4Hz, 6 - H), 4.57 (s, $PhOCH_2$), 5.25 (s,CO_2CH_2 Ph), 5.38 (dd, J 8 and 4Hz, 7 - H), 5.63 (d, J 2.5 Hz, collapses to s on D_2O exch, 2β - H), 6.23 br (s, ring NH), 6.9-7.5 (m, aromatics), and 7.20 (d, J 8Hz, side-chain NH), and (14) ν_{max} ($CHCl_3$) 3400 (amides), 1785 (β-lactam), 1755 (ester), and 1680 (amides) cm^{-1}; δ($CDCl_3$) 2.49 and 2.62 (ABq, J 17Hz, higher field arm further coupled, d, J 6Hz; lower field arm further coupled, d, J 9Hz), 4.17 (ddd, J 9, 6 and 4.5 Hz, 6-H), 4.54 (s, $PhOCH_2$), 5.16 br (s, becomes dd, J 1.3Hz on D_2O exch., 2α-H), 5.23 and 5.28 (ABq, J 12 Hz, CO_2CH_2Ph), 5.43 (ddd, J 8, 4.5 and 1.3 Hz, 7 - H), 6.88 br (s, ring NH), 6.9-7.5 (m, aromatics), and 7.73 (d, J 8Hz, side-chain NH).



(13) $R^1 = CO_2CH_2Ph$, $R^2 = H$
(14) $R^1 = H$, $R^2 = CO_2CH_2Ph$
(15) $R^1 = CO_2H$, $R^2 = H$
(16) $R^1 = H$, $R^2 = CO_2H$

Catalytic hydrogenation of (13) and (14) provided (15) and (16) respectively. The acid (16) possessed weak gram-positive activity, the minimum inhibitory concentrations (μg/ml) against B. subtilis, Staph. aureus (Oxford), and Staph. aureus (Russell) [10], being 25, 25, and 200 respectively. The epimeric acid (15) was much less active, the corresponding figures being 200, 100, and >200. Although unexpected, the observation that the epimer with the opposite carboxylate configuration to that found in naturally occurring penicillins is more active is in agreement with a previous report[6] concerning the activity of 3-oxa-8-oxo-1-azabicyclo [4.2.0] octane-2-carboxylic acids.

References and Notes

1. For part 3 in this series see M.J.Pearson, preceding paper.

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. J.G.Gleason, D.B.Bryan, and K.G.Holden, Tetrahedron Lett., 1980, 3947.

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

6. J.G.Gleason, T.F.Buckley, K.G.Holden, D.B.Bryan, and P.Siler, J.Am.Chem.Soc. 1979, 101, 4730.

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8. J.E.McMurray, J.Melton, and H.Padgett, J.Org.Chem., 1974, 39, 259.

9. D.O.Spry, Tetrahedron Lett., 1973, 165; T.Kamiya, T.Teraji, M.Hashimoto, O.Nakaguchi, and T.Oku, J.Am.Chem.Soc., 1976, 98, 2343; M.Aratani and M.Hashimoto, J.Am.Chem.Soc. 1980, 102, 6171; M.J.Pearson and D.Davies, J.Chem.Soc.Perkin Trans.1, 1981, 2539.

10. β-Lactamase producing strain.

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