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# SYNTHESIS OF NOVEL FUSED β-LACTAMS BY INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS.6[1]. PHENOXYACETAMIDO ISO-AZAPENEM AND ISO-AZACEPHEM CARBOXYLIC ACIDS.

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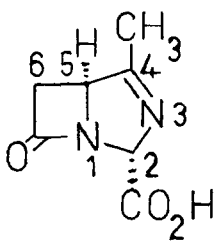
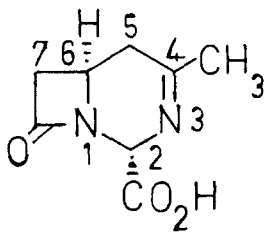
Summary: 6-Phenoxyacetamido-7-oxo-1,3-diazabicyclo [3.2.0] hept-3-ene-2-carboxylic acid (9) and 7-phenoxyacetamido-8-oxo-1,3-diazabicyclo [4.2.0] oct-3-ene-2-carboxylic acid (22) have been prepared and shown to be devoid of antibacterial activity.

It has recently been disclosed[2] that the 1,3-diazabicyclo [3.2.0] hept-3-ene and 1,3-diazabicyclo [4.2.0] oct-3-ene systems (1) and (2) possess no interesting biological activity. Subsequent to our report, similar compounds have been described by Nagakura[3], and this has prompted us to present our further studies in this area, aimed at the synthesis of the corresponding 6- and 7-acylamino derivatives.

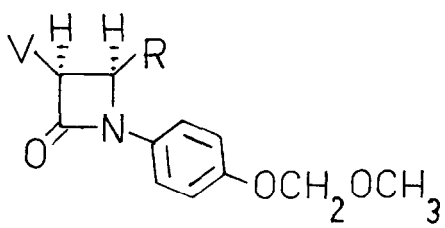


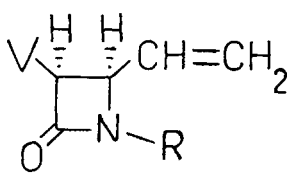
(1)



(2)

Catalytic semi-hydrogenation of the acetylene (3)[1,4] (10% Pd-$BaSO_4$, dioxane-pyridine) gave the olefin (4)[5], which was deblocked with ceric ammonium nitrate[6] to afford the azetidinone (5).





(3) R = C ≡ CH

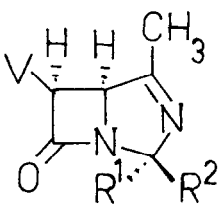
(4) R = CH = $CH_2$

(5) R = H

(6) R = $CHN_3CO_2CH_2Ph$

V = $PhOCH_2CONH$

Conversion[2] of (5) to the azide (6) and cyclisation (34h, refluxing toluene) gave (7)[7], mp 117°C (dec), $\nu_{max}(CHCl_3)$ 3400, 1805, 1755, 1700 and 1630 $cm^{-1}$; $\delta(CHCl_3)$ (250MHz) 2.06 (m, fine coupling to 2-H and 5-H, Me), 4.56 (s, $PhO\underline{CH_2}$), 4.81 (m, irradiation at δ2.06 gives dd, J 5.8 and 3.2 Hz, 5-H), 5.15 and 5.23 (ABq, J 12Hz, $CO_2\underline{CH_2}Ph$), 5.67 (dd, J8 and 5.8 Hz, 6-H), 6.14(m, irradiation at δ2.06 gives d, J 3.2 Hz, 2-H) and 6.85-7.4(m, aromatics) and (8)[7], $\nu_{max}(CHCl_3)$ 3400, 1805, 1755, 1695, and 1638$cm^{-1}$; $\delta(CHCl_3)$ (250 MHz) 2.04(m, fine coupling to 2-H and 5-H, Me), 4.56(s, $PhO\underline{CH_2}$), 4.65 (m, irradiation at δ2.04 gives dd, J 5.5 and 3.3Hz, 5-H), 5.27 and 5.34 (ABq, J 12Hz, $CO_2\underline{CH_2}Ph$), 5.42 (m, irradiation at 2.04 gives dd, J 3.3 and 1.2 Hz, 2-H), 5.68 (ddd, J 8.1, 5.5, and 1.2 Hz), and 6.85-7.5 (m, aromatics).



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

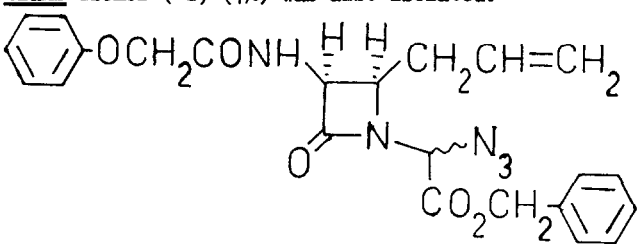
(8) $R^1 = H$, $R^2 = CO_2CH_2Ph$

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

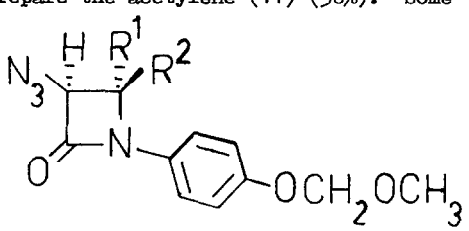
V = $PhOCH_2CONH$

Hydrogenation of (7) then afforded (9), which was devoid of antibacterial activity. The isomer (8) with the unnatural penicillin stereochemistry at C-2 decomposed on hydrogenation.

For the homologous series the olefin (10)[8] was the desired key intermediate. Standard ketene-imine cycloaddition methodology[9] was used to prepare the acetylene (11) (58%). Some trans-isomer (12) (7%) was also isolated.



(10)



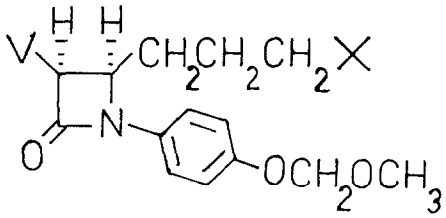
(11) $R^1 = H$, $R^2 = C\equiv C\text{-}CH_2OSiPh_2Bu^t$

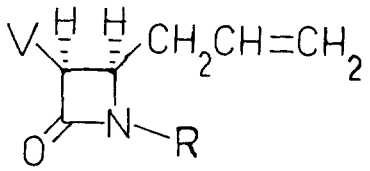
(12) $R^1 = C\equiv C\text{-}CH_2OSiPh_2Bu^t$, $R^2 = H$

(13) $R^1 = H$, $R^2 = C\equiv C\text{-}CH_2OH$

Reduction[10] of (11) followed by acylation, and removal of the hydroxyl protecting group gave the alcohol (13). The triple bond was hydrogenated to provide (14), which was readily mesylated to afford (15) [50% overall from (11)]. Since β-elimination[11] to the olefin (18) was not successful, the mesylate (15) was converted into the selenide (16) by treatment with sodium 2-nitrophenylselenide. The selenide (16) was not isolated but oxidised in situ with m-chloroperbenzoic acid to give the selenoxide (17), which underwent slow elimination (R.T.,24h) to afford the olefin (18) (40%)[12]. The β-lactam nitrogen was then deblocked[6] to give the

azetidinone (19), m.p. 153-154°C; $\nu_{max}$ (Nujol) 3300, 1765, 1755, and 1665cm$^{-1}$; $\delta(CDCl_3)$ (250 MHz) inter alia 3.95 (ddd, J 8.4, 5, and 4.5Hz, 4-H), 4.54 (s, $PhOC\underline{H}_2$), 5.37 (ddd, J 8.5, 5, and 1.2Hz, 3-H) and 6.23br (s, β-lactam N<u>H</u>).





(14) X = OH

(15) X = $OSO_2Me$

(16) X = Se-$C_6H_4$-o-$NO_2$

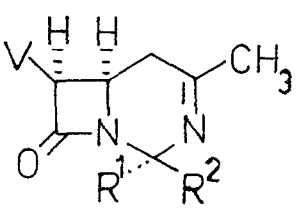
(17) X = Se(O)-$C_6H_4$-o-$NO_2$

(18) R = $C_6H_4$-p-$OCH_2OCH_3$

(19) R = H

V = $PhOCH_2CONH$

The azide (10) was prepared[2] and heated in toluene for 7h to give (20) (22%)[7], $\nu_{max}$ ($CHCl_3$) 3420, 1770, 1760, 1695, and 1660cm$^{-1}$; $\delta(CDCl_3)$ (250 MHz) inter alia 2.04 (d, J ca. 1.5Hz, Me), 4.02 (ddd, J 8,6, and 4.5 Hz, 6-H), 4.56(s, $PhOC\underline{H}_2$), 5.32 (dd, J 6 and 4.5 Hz, 7-H), and 5.77br (s, 2-H), and (21) (7%)[7,13], $\nu_{max}$($CHCl_3$) 3420, 1770, 1765, 1690 and 1660 sh cm$^{-1}$; $\delta(CDCl_3)$ (250 MHz) inter alia 2.09 (d, J ca. 2Hz, Me), 3.85(ddd, J 10,6, and 5Hz, 6-H), 4.56(s, $PhOC\underline{H}_2$), 5.2-5.35 (partially obscured m, 7-H), and 5.40 (m, 2-H).



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

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

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

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

V = $PhOCH_2CONH$

The free acids (22) and (23) were found to be antibacterially inactive.

References and Notes


1. Part 5, C.L. Branch, S.C. Finch, and M.J.Pearson, in the press.
2. C.L.Branch and M.J.Pearson, J. Chem.Soc. Chem. Commun., 1981, 946.
3. I.Nagakura, Heterocycles, 1981, 16, 1495.
4. All synthetic compounds are racemic mixtures, but only one enantiomer is depicted for convenience.
5. All new compounds were fully characterised spectroscopically and gave correct elemental analyses and/or molecular ion, high resolution mass measurement.
6. T. Fukuyama, R.K. Frank, and C.F.Jewell,Jr., J. Am. Chem. Soc., 1980, 102, 2122.
7. The assignments of configuration parallel those made on the basis of shift values of the C-2 proton for the corresponding derivatives lacking the acylamino side chain.
8. While our work was in progress the synthesis of some related intermediates was described, H.Onoue, M.Narisada, S.Uyeo, H.Matsumura, K.Okada, T.Yano, and W.Nagata, Tetrahedron Lett., 1979, 3867.
9. A.K.Bose, J.C.Kapur, S.D.Sharma, and M.S.Manhas, Tetrahedron Lett., 1973, 2319. The azidoketene precursor was reacted with the Schiff base derived from p-methoxymethoxyaniline (see Ref.6) and 4-t-butyldiphenylsilyloxybut-2-yn-1-al (prepared by treatment of propyn-3-ol with t-butyldiphenylsilyl chloride/imidazole in DMF, followed by the introduction of the formyl group [H.Hauptmann and M.Mader, Synthesis, 1978, 307])
10. T.W. Doyle, B.Belleau, B-Y. Luh, C.F. Ferrari, and M.P. Cunningham, Can. J. Chem., 1977, 55, 468.
11. Various conditions and bases, including 3,3,6,9,9-pentamethyl-2,10-diazabicyclo [4.4.0]-1-decene (F. Heinzer, M. Soukap, A. Eschenmoser, Helv. Chem. Acta., 1978, 61, 2851) were used.
12. Large quantities of mesylate (15) (50-60%)were always recovered from this reaction, owing to inefficient conversion of (15) into the selenide (16).
13. Complete purification of this isomer was not possible since it showed some instability to chromatography, and could not be crystallised. Similar problems were encountered in the 7-unsubstituted series (see Ref.2).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