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CHEMICAL MODIFICATION OF THE OLIVANIC ACIDS: SYNTHESIS OF SUBSTITUTED 6-[1-(1,2,3-TRIAZOL-1-YL)ETHYL] CARBAPENEM DERIVATIVES

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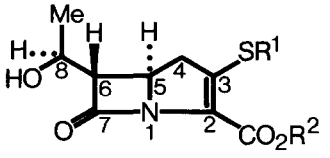
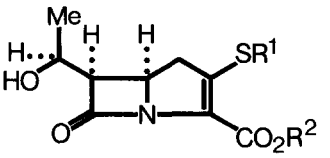
Summary: The 1,3-dipolar cycloaddition of activated acetylenes to 6-(1-azidoethyl) olivanic acid derivatives afforded the corresponding 6-[1-(1,2,3-triazol-1-yl)ethyl] compounds.

The olivanic acids, MM 22380 (5), MM 22381 (1), MM 22382 (6) and MM 22383 (2), together with thienamycin, the carpetimycins, and PS-5, are members of a family of β-lactam antibiotics, all of which were isolated from soil microorganisms.[1,2] The exceptional broad spectrum antibacterial potency of this class of compounds has prompted considerable effort in their chemical modification in order to determine the structural requirements for optimum activity.





(1) MM 22381; R^1=CH_2CH_2NHAc, R^2=H

(2) MM 22383; R^1=CH=CHNHAc (t), R^2=H

(3) R^1=CH_2CH_2NHAc, R^2=PNB

(4) R^1=CH=CHNHAc (t), R^2=PNB

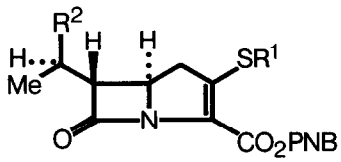
(5) MM 22380; R^1=CH_2CH_2NHAc, R^2=H

(6) MM 22382; R^1=CH=CHNHAc (t), R^2=H

(7) R^1=CH=CHNHAc (t), R^2=PNB

PNB = p-nitrobenzyl

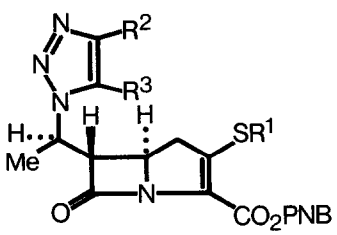
A recent report[3] from these laboratories described the preparation of p-nitrobenzyl (5R,6S)-3-(2-acetamidoethylthio)-6-[(R)-1-azidoethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8) and the corresponding 3-[(E)-2-acetamidovinylthio]-analogue (9) by reaction of the p-nitrobenzyl esters of MM 22381 (3) and MM 22383 (4), respectively, with hydrazoic acid, triphenylphosphine, and diethyl azodicarboxylate. The present communication describes the synthesis of a series of novel 6-[1-(1,2,3-triazol-1-yl)ethyl] carbapenem[4] derivatives by way of the 1,3-dipolar cycloaddition of azido-derivatives (8) and (9) to activated acetylenes.

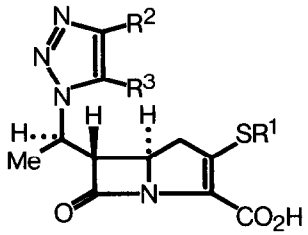


(8) R^1 = CH_2CH_2NHAc, R^2 = N_3

(9) R^1 = CH $\overset{t}{=}$ CHNHAc, R^2 = N_3

(10) R^1 = CH $\overset{t}{=}$ CHNHAc, R^2 = NHAc





(11) R^1=CH_2CH_2NHAc, R^2=R^3=CO_2Me

(12) R^1=CH_2CH_2NHAc, R^2=CO_2PNB, R^3=H

(13) R^1=CH_2CH_2NHAc, R^2=H, R^2CO_2PNB

(14) R^1=CH $\overset{t}{=}$ CHNHAc, R^2=R^3=CO_2Me

(15) R^1=CH $\overset{t}{=}$ CHNHAc, R^2=CO_2PNB, R^3=H

(16) R^1=CH $\overset{t}{=}$ CHNHAc,
R^2=$CO_2CH_2CH_2NHCO_2PNB$, R^3=H

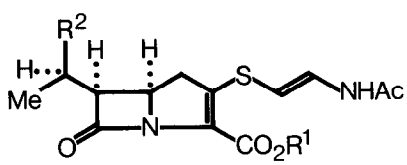
(17) R^1=CH_2CH_2NHAc, R^2=R^3=CO_2Me

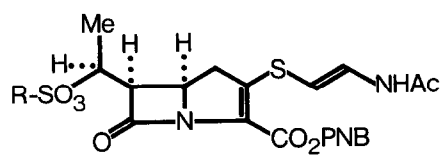
(18) R^1= CH_2CH_2NHAc, R^2=CO_2H, R^3=H

(19) R^1=CH $\overset{t}{=}$ CHNHAc, R^2=R^3=CO_2Me

(20) R^1=CH $\overset{t}{=}$ CHNHAc, R^2=CO_2H, R^3=H

(21) R^1=CH $\overset{t}{=}$ CHNHAc, R^2=$CO_2CH_2CH_2NH_2$
R^3=H



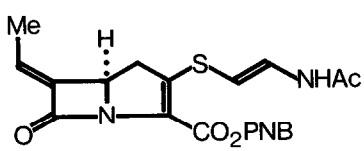


(22) R^1 = PNB, R^2 = N_3

(23) R^1 = H, R^2 = NH_2

(24) R = CH_3

(25) R = p-NO_2-C_6H_4



(26)

PNB = p-nitrobenzyl

The cycloaddition reactions were effected by heating a solution of the azide and the substituted acetylene in toluene to reflux (6-24 h). Reaction of (8) with dimethyl acetylenedicarboxylate afforded the 6-[1-(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)ethyl] compound (11) in 71% yield. Similar treatment of the azido-derivative bearing the unsaturated C-3 side-chain (9) with dimethyl acetylenedicarboxylate gave the triazole (14) in 62% yield after silica gel column chromatography.

Addition of p-nitrobenzyl propiolate to the azide (8) provided a mixture of isomeric triazoles (6:1), in 56% isolated yield. The orientation in the addition of azides to unsymmetrical acetylenes is controlled by both steric and electronic factors. In general, the 1,3-dipolar cycloaddition of azides to unsymmetrical acetylenes bearing an electron withdrawing substituent yields predominantly that isomer with the electron withdrawing group at the 4-position of the triazole.[5] On this basis it was assumed that the major isomer was the 4-substituted triazolo-derivative (12) and the minor isomer the 5-substituted triazolo-derivative (13). In contrast, the addition of (9) to both p-nitrobenzyl propiolate and 2-(N-p-nitrobenzyloxycarbonyl)aminoethyl propiolate gave essentially one product in each case. They were considered to be the 4-substituted triazolo-derivatives (15) and (16), and were isolated in 50% and 25% yield, respectively. Only traces of the other regio-isomers could be detected by n.m.r. spectroscopy.

Removal of the carboxy and amino protecting groups was accomplished by catalytic hydrogenolysis (H_2, 5% Pd/C, aqueous 1,4-dioxan, r.t., 3 h). Esters (11) and (14) afforded the monosodium salts of (17) and (19), (1 equiv.$NaHCO_3$) (yields 59% and 49% respectively[6]). Similar deprotection of the esters (12) and (15) provided the disodium salts of (18) and (20), (yields 75% and 74% respectively[6]) (2 equiv. $NaHCO_3$). Lyophilisation of the aqueous solutions after Biogel® P-2 column chromatography gave white solids. Hydrogenolysis of (16) in the presence of pH 7.0, 0.05M phosphate buffer gave an aqueous solution containing the amino-acid (21) in 54% yield.[6,7]

Other reactions of the azido-group were briefly examined. Elaboration of the azido-derivative (9) to the 6-(1-acetamidoethyl) carbapenem (10) was achieved, albeit in low yield, by means of the phosphinimine-acylation reaction sequence:[8] (i) Ph_3P, toluene, 100°C, 2 h, (ii) CH_3COCl, r.t., 10 min, (iii) $NaHCO_3$, aqueous THF, r.t., 16 h. Catalytic hydrogenolysis of (10), however, failed to yield a β-lactam containing product.

Attempts to prepare the azidoethyl derivative with the (5R,6R,8R)-stereochemistry (22), by reaction of the ester (7) with triphenylphosphine and diethyl azodicarboxylate in the presence of hydrazoic acid met with little success. Both in this reaction, and that of the mesylate (24) with sodium azide (DMF, r.t.), the ethylidene (26) was the sole product. The azide (22) was eventually prepared via the p-nitrobenzenesulphonate (25),[9]

which was prepared in 9% yield[10] by the reaction of (7) with p-nitrobenzenesulphonyl chloride (N-methylmorpholine, 4-dimethylaminopyridine, THF, r.t., 18 h). Treatment of (25) with sodium azide in DMF (r.t., 2 h) afforded the ester (22) in 24% yield. Competitive E2-elimination of p-nitrobenzenesulphonic acid from (25) accounted for the formation of the ethylidene (26), isolated from the reaction mixture in 19% yield. Catalytic hydrogenolysis of (22) in the presence of pH 7.0, 0.05M phosphate buffer (2 h) was instrumental in both removing the carboxylic acid protecting group and reducing the azido function to an amino group, thus providing an aqueous solution of the amino-acid (23) in 25% yield.[6,7]

Most of the novel salts displayed good levels of activity against a broad range of Gram-positive and Gram-negative bacteria.

References and Notes

1. A.G. Brown, D.F. Corbett, A.J. Eglington, and T.T. Howarth, J. Antibiot., 1979, 32, 961.

2. R.W. Ratcliffe and G. Albers-Schönberg, 'Chemistry and Biology of β-Lactam Antibiotics', Vol. 2, 227, Ed. R.B. Morin and M. Gorman, Academic Press 1982.

3. D.F. Corbett, S. Coulton, and R. Southgate, J. Chem. Soc., Perkin Trans. I, 1982, 3011.

4. For nomenclature of β-lactam antibiotics, see A.G. Brown, J. Antimicrobial Chemotherapy, 1982, 10, 365.

5. For review of 1,2,3-triazoles, see T.L. Gilchrist and G.E. Gymer, Adv. Heterocycl. Chem., 1974, 16, 33-85.

6. Yields were based on ε8,500 at λmax 299nm in the u.v. spectrum for the acetamidoethylthio-derivatives and ε14,000 at λmax 308nm for the acetamidovinylthio-derivatives.

7. Isolation of the amino-acids by lyophilisation often resulted in considerable degradation. They were therefore prepared as aqueous solutions for antibacterial evaluation. Their presence in solution was inferred by the characteristic olivanic acid u.v. absorption maxima, λmax 298nm for the acetamidoethylthio-derivatives and λmax 308nm for the acetamidovinylthio-derivatives (see reference 1).

8. M.D. Bachi and J. Vaya, J. Org. Chem., 1979, 44, 4393.

9. The p-nitrobenzenesulphonate ester (25) was unstable and formed the ethylidene (26) on standing.

10. The starting ester (7) could be recovered in 60% yield after silica gel column chromatography.

11. All new compounds had satisfactory microanalytical data and/or spectroscopic properties.

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