

Communications to the editor

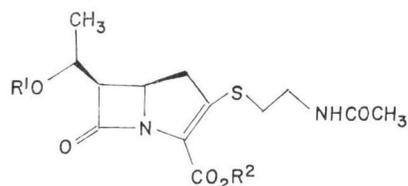
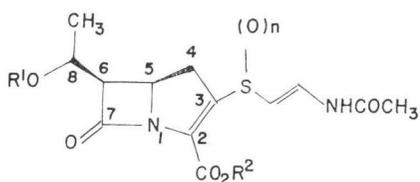
STRUCTURES OF OLIVANIC ACID
DERIVATIVES MM 22380,
MM 22381, MM 22382
AND MM 22383;
FOUR NEW ANTIBIOTICS ISOLATED
FROM *STREPTOMYCES OLIVACEUS*

Sir:

Recent communications from these laboratories have described the isolation¹⁾ and structure elucidation^{2,3)} of the olivanic acid²⁾ derivatives MM 13902 (1), MM 4550 (2) and MM 17880 (3).

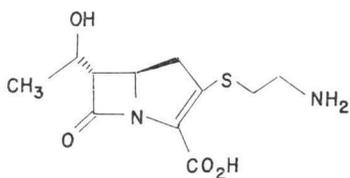
Together with thienamycin (4)⁴⁾ and PS-5(5)⁵⁾* these metabolites comprise a family of naturally occurring antibiotics containing the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system (6). We now report the structures of four new members of this family, MM 22380 (7), MM 22381 (8), MM 22382 (9) and MM 22383 (10), isolated from *Streptomyces olivaceus*⁶⁾.

The antibiotics were all isolated as freeze-dried mono-sodium salts (11)~(14), each of which showed a β -lactam carbonyl absorption at 1750 cm^{-1} in the i.r. (KBr) spectrum. The u.v.

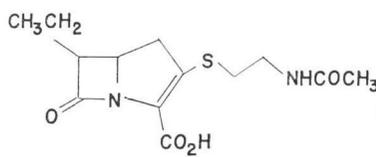


- (1) $R^1 = \text{SO}_3\text{H}$, $R^2 = \text{H}$, $n = 0$
 (2) $R^1 = \text{SO}_3\text{H}$, $R^2 = \text{H}$, $n = 1$
 (9) $R^1 = \text{H}$, $R^2 = \text{H}$, $n = 0$
 (13) $R^1 = \text{H}$, $R^2 = \text{Na}$, $n = 0$
 (17) $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{C}_6\text{H}_4(\text{NO}_2)-p$, $n = 0$

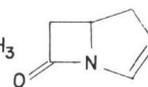
- (3) $R^1 = \text{SO}_3\text{H}$, $R^2 = \text{H}$
 (7) $R^1 = \text{H}$, $R^2 = \text{H}$
 (11) $R^1 = \text{H}$, $R^2 = \text{Na}$
 (15) $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{C}_6\text{H}_4(\text{NO}_2)-p$



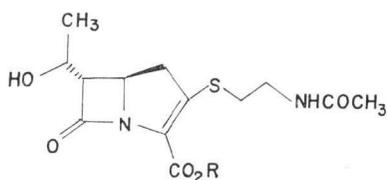
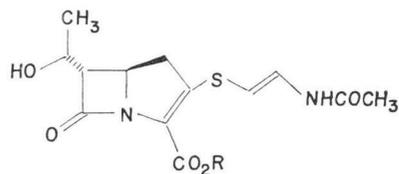
(4)



(5)



(6)

(8) $R = \text{H}$ (12) $R = \text{Na}$ (16) $R = \text{CH}_2\text{C}_6\text{H}_4(\text{NO}_2)-p$ (10) $R = \text{H}$ (14) $R = \text{Na}$ (18) $R = \text{CH}_2\text{C}_6\text{H}_4(\text{NO}_2)-p$

* The stereochemistry of this molecule has not been described.

spectra of MM 22380 and MM 22381 (Table 1) contained the characteristic long-wavelength chromophore of other olivanic acids as typified by MM 17880 (3), whilst the additional lower-wavelength absorption observed in the spectra of MM 22382 and MM 22383 was similar to that present in MM 13902 (1). The ^1H n.m.r. spectra (D_2O) of the sodium salts of MM 22382 (13) and MM 22383 (14) revealed the presence of a *trans*, disubstituted double bond ($J=14\text{ Hz}$) which was absent in MM 22380 and MM 22381.

Alkylation of each of the sodium salts with *p*-nitrobenzyl bromide in dimethylformamide afforded the *p*-nitrobenzyl esters* [(15), m.p. $166\sim 168^\circ\text{C}$], [(16), m.p. $163\sim 165^\circ\text{C}$], [(17), m.p. $175\sim 177^\circ\text{C}$] and [(18), m.p. $191\sim 193^\circ\text{C}$]. Field-desorption mass spectral studies indicated that the *p*-nitrobenzyl esters of MM 22382 (17) and MM 22383 (18) both possessed a molecular weight of 447, whilst the corresponding esters of MM 22380 (15) and MM 22381 (16) each contained two additional hydrogen atoms (m/e , 449). These results, combined with analytical data on the *p*-nitrobenzyl esters, allowed a molecular formula of $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$ to be assigned to both MM 22380 and MM 22381, and $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$ to MM 22382 and MM 22383.

It was apparent from the above evidence that the four new compounds consisted of two pairs of isomers, one pair related to MM 13902 (1) having the *E*-2-acetamidoethylthio side-chain, and the other pair related to MM 17880 (3) with the corresponding saturated side-chain. Furthermore, from the molecular composition of the new metabolites it appeared that the sulphate moiety of MM 13902 and MM 17880 was absent and replaced by a hydroxyl-function. Further confirmation of this came from the i.r. spectra (KBr) of the *p*-nitrobenzyl esters (15)~(18), all of which lacked the characteristic sulphate absorption ($1220\sim 1270\text{ cm}^{-1}$), and the corresponding ^1H n.m.r. spectra [$(\text{CD}_3)_2\text{NCDO}$] which all exhibited an exchangeable hydroxyl proton. The gross structure of MM 22380 and MM 22381 was thus established as 3-(2-acetamidoethylthio)-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid and that of MM 22382 and MM 22383 as 3-[(*E*)-2-

Table 1. U.V. Spectra of olivanic acids*.

Compound	λ_{max} (H_2O)
MM 17880 (3)	298 (ϵ 8410)
MM 13902 (1)	307 (ϵ 15,520), 227 (ϵ 14,650)
MM 22380 (7)	298 (ϵ 8131)
MM 22381 (8)	301 (ϵ 7930)
MM 22382 (9)	308 (ϵ 13,627), 228 (ϵ 13,360)
MM 22383 (10)	309 (ϵ 13,933), 229 (ϵ 13,933)

* Determined as sodium salts.

acetamidoethylthio]-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

The configuration of the β -lactam hydrogen atoms in MM 13902 (1), MM 4550 (2) and MM 17880 (3) was determined to be *cis* by virtue of the observed coupling constants ($J_{5,6}=5.5\sim 6.0\text{ Hz}$) in the n.m.r. spectra^{2,3}. The smaller coupling ($J_{5,6}=3\text{ Hz}$) in thienamycin and its derivatives⁴ is characteristic of a *trans* β -lactam configuration. It was apparent from the ^1H n.m.r. spectra of the sodium salts (11)~(14) (D_2O) and the corresponding esters (15)~(18) [$(\text{CD}_3)_2\text{NCDO}$] that the β -lactam protons in MM 22380 and MM 22382 possessed the larger coupling ($J_{5,6}=5.5\sim 6.0\text{ Hz}$), whereas the smaller coupling ($J_{5,6}=3\text{ Hz}$) was observed in MM 22381 and MM 22383. MM 22380 (7) and MM 22382 (9) therefore contain a *cis*-oriented β -lactam and have the 5*R*, 6*R*-configuration**, and MM 22381 (8) and MM 22383 (10) each possess a *trans* β -lactam with the 5*R*, 6*S*-configuration.

X-Ray analysis of the *p*-nitrobenzyl ester of MM 22383 (18) confirmed the gross structure and established the configuration at C-8 to be *S*, the same as MM 13902, MM 4550 and MM 17880¹ but opposite to that of thienamycin⁴. MM 22380, MM 22381 and MM 22382 would therefore also be expected to possess the 8*S*-configuration and this was subsequently confirmed by chemical means (to be reported in a future paper). MM 22380 (7) and MM 22382 (9) are therefore desulphonated analogues of MM 17880 (3) and MM 13902 (1), respectively; MM 22381 (8) and MM 22383 (10) in contrast both possess a *trans* β -lactam as in thienamycin (4) but differ from the latter by virtue of the

* Spectral properties and elemental analyses were in accord with the proposed structures.

** All configurations are based on the assumption

that the absolute configuration at C-5 is *R* as in all other known naturally occurring β -lactam antibiotics.

opposite configuration at C-8. The epithienamycins⁴⁾ have similar gross structures to the olivanic acid derivatives (7)~(10) but their stereochemistry has not been described in detail.

Compounds (7)~(10) all exhibit a broad spectrum of antibacterial activity and also possess β -lactamase inhibitory properties.

Acknowledgment

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