Conversion of the Olivanic Acids into Antibiotics of the PS-5 Type: Use of a New Carboxy Protecting Group

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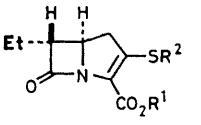
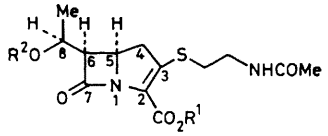
Summary The syntheses of PS-5 (**1**) and analogues from the olivanic acids MM 17880 (**4**) and MM 13902 (**10**), including the use of a new carboxy protecting group, the *p*-methoxycarbonylbenzyl group, are reported together with the chemical elucidation of the stereochemistry at C-8 of the olivanic acids.

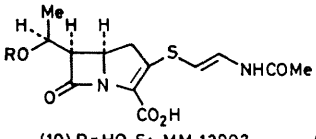
WE have recently reported the structural elucidation of some new potent β-lactam antibiotics, the olivanic acids[1-3] possessing the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system. Some aspects of the chemistry of these antibiotics establishing their stereochemical interrelationships and their conversion into the antibiotics PS-5[4] (**1**) and PS-7[5] (**2**) are now described. We also report the use of a new carboxy protecting group, the *p*-methoxycarbonylbenzyl group.†



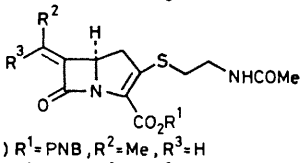
(1) R^1 = H, R^2 = $CH_2CH_2NHCOMe$
(2) R^1 = H, R^2 = $CH{=}CHNHCOMe$
(3) R^1 = PNB, R^2 = $CH_2CH_2NHCOMe$



(4) R^1 = H, R^2 = HO_3S; MM 17880
(5) R^1 = PNB, R^2 = EtO_3S
(6) R^1 = Na, R^2 = NaO_3S
(7) R^1 = PNB, R^2 = $MeSO_2$
(8) R^1 = PNB, R^2 = H
(9) R^1 = PMCB, R^2 = NaO_3S



(10) R = HO_3S; MM 13902
(11) R = H; MM 22382

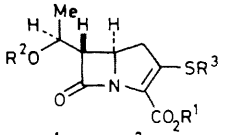


(12) R^1 = PNB, R^2 = Me, R^3 = H
(13) R^1 = PNB, R^2 = H, R^3 = Me
(14) R^1 = PMCB, R^2 = Me, R^3 = H

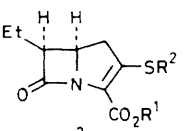
PNB = $CH_2C_6H_4NO_2$-*p*
PMCB = $CH_2C_6H_4CO_2Me$-*p*

The ethyl sulphate *p*-nitrobenzyl carboxylate (**5**) of MM 17880 was prepared from the corresponding disodium salt (**6**)[2] by esterification with *p*-nitrobenzyl bromide (DMF;† r.t.), ion pair extraction [$PhCH_2(Me)_2(C_{16}H_{33})$-$N^+Cl^-$; CH_2Cl_2–H_2O], and alkylation ($Et_3O^+BF_4^-$; CH_2Cl_2). Elimination of sulphate from (**5**) (K_2CO_3; DMF; r.t.) gave the (*E*)-ethylidene derivative (**12**) (45%). Similarly the mesylate (**7**), derived ($MeSO_2Cl$; Et_3N; CH_2Cl_2) from the *p*-nitrobenzyl ester (**8**) of MM 22380,[3] afforded the (*E*)-ethylidene derivative (**12**), but the mesylate (**15**), derived from MM 22381 (**16**)[3] yielded the (*Z*)-ethylidene derivative (**13**). Assuming the reactions proceed *via* an *E*2 elimination in the normal *anti*-manner it follows that the relative stereochemistry between C-6 and C-8 in MM 22381 (**16**) differs from that in MM 17880 (**4**) and MM 22380 (*cf.* **8**). Since the stereochemistry is (5*R*,6*R*) in (**4**) and (**8**), and (5*R*,6*S*) in (**16**)[3] it follows that the configuration at C-8 is (*S*) in all the three metabolites. In the same way the C-8 stereochemistry of the other olivanic acids, MM 13902 (**10**), MM 22382 (**11**), and MM 22383 (**17**) was shown to be (*S*).

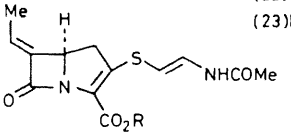
Hydride reduction ($NaBH_4$; aq. THF;† 3 °C) of the ethylidene group in (**12**) gave predominantly the *trans*-β-lactam (**3**) (30%) together with a little of the *cis*-compound (**18**) (ratio *ca.* 9:1). Hydrogenolysis (5% Pd–C; aq. dioxan) of the *p*-nitrobenzyl ester in (**3**) afforded the deoxy-derivative (**1**) (PS-5), isolated as its sodium salt The dehydro-derivative (**2**) (PS-7) was obtained by a similar sequence of reactions from MM 13902 (**10**).



(15) R^1 = PNB, R^2 = $MeSO_2$
R^3 = $CH_2CH_2NHCOMe$
(16) R^1 = R^2 = H, R^3 = $CH_2CH_2NHCOMe$
(17) R^1 = R^2 = H, R^3 = $CH{=}CHNHCOMe$



(18) R^1 = PNB, R^2 = $CH_2CH_2NHCOMe$
(19) R^1 = CH_2Ph, R^2 = $CH{=}CHNHCOMe$
(20) R^1 = PNB, R^2 = $CH{=}CHNHCOMe$
(21) R^1 = PMCB, R^2 = $CH_2CH_2NHCOMe$
(22) R^1 = H, R^2 = $CH_2CH_2NHCOMe$
(23) R^1 = H, R^2 = $CH{=}CHNHCOMe$



(24) R = CH_2Ph
(25) R = PNB

PNB = $CH_2C_6H_4NO_2$-*p*
PMCB = $CH_2C_6H_4CO_2Me$-*p*

In contrast to hydride reduction, catalytic hydrogenation of the 6-ethylidene derivatives gave predominantly the *cis*-6-ethyl isomer. Thus for example (**24**), derived from the monobenzyl ester of MM 13902, gave (H_2; PtO_2; EtOAc; 24 h) largely the *cis*-6-ethyl derivative (**19**) together with a little of the corresponding *trans*-6-ethyl isomer (*ca.* 4:1). Under the same conditions the *p*-nitrobenzyl ester (**25**) failed to give the desired *cis*-6-ethyl derivative (**20**) in acceptable yield. Attempts at removing the benzyl group from (**19**) also proved unsuccessful, and as quantities of the carboxylic acid were required for biological evaluation another protecting group was developed.

p-Methoxycarbonylbenzyl acetate is known to be cleaved electrochemically[6]; thus the use of the *p*-methoxycarbonylbenzyl† esters of the olivanic acids was investigated. Accordingly, the PMCB ester of MM 17880 (**9**),

† PMCB = *p*-methoxycarbonylbenzyl; PNB = *p*-nitrobenzyl; DMF = dimethylformamide; THF = tetrahydrofuran.

‡ New compounds reported were satisfactorily characterised by microanalytical and/or spectroscopic data.

prepared by alkylation of the disodium salt (**6**) with methyl 4-bromomethylbenzoate, was converted into the ethylidene derivative (**14**) Hydrogenation yielded the *cis*-6-ethyl derivative (**21**) (30%) Cleavage of the ester group was effected by reduction at a Hg cathode (−1 9 V *vs* standard calomel electrode) in a divided cell (Pt anode, 0·1M $Bu^n_4NBF_4$; DMF) After removal of DMF the catholyte was partitioned between CH_2Cl_2 and aqueous $NaBF_4$ to afford the sodium salt of (**22**) (6-*epi* PS-5) in the aqueous layer The sodium salt of (**22**) was purified by chromotography on Biogel P-2 A similar sequence of reactions from MM 13902 (**10**) gave the sodium salt corresponding to the dehydro-derivative (**23**) (6-*epi* PS-7)

All four derivatives (**1**), (**2**), (**22**), and (**23**) showed a high level of antibacterial activity Racemic (**1**) and (**22**) have been prepared in these laboratories by a totally synthetic route [7]

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[1] A G Brown, D F Corbett, A J Eglington, and T T Howarth, *J Chem Soc , Chem Commun* , 1977, 523
[2] D F Corbett, A J Eglington, and T T Howarth, *J Chem Soc , Chem Commun* , 1977, 954
[3] A G Brown, D F Corbett, A J Eglington, and T T Howarth, *J Antibiotics*, 1979, **32**, 961
[4] K Okamura, S Hirata, Y Okumura, Y Fukagawa, Y Shimauchi, K Kouno T Ishikura, and J Lein, *J Antibiotics*, 1978, **31**, 480
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[6] J P Coleman, H G Gilde, J H P Utley, and B C L Weedon, *Chem Commun* , 1970, 738
[7] J H Bateson, R I Hickling, P M Roberts, T C Smale, and R Southgate, *J Chem Soc , Chem Commun* , 1980, following communication