Tetrahedron Letters No. 13, pp. 1025-1028, 1970. Pergamon Press. Printed in Great Britain.

MACROLIDE ANTIBIOTIC STUDIES. XIII*
PARTIAL ABSOLUTE CONFIGURATIONS OF METHYMYCIN, NEOMETHYMYCIN, NARBOMYCIN AND PICROMYCIN

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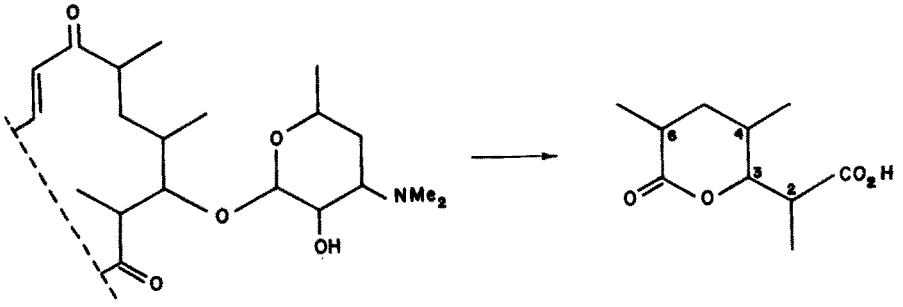
(Received in UK 6 February 1970; accepted for publication 12 February 1970)

Oxidative degradation of the macrolide antibiotics[1] methymycin[2], neomethymycin[3], narbomycin[4], and picromycin[5], all of which contain the structural segment (I), yields the (+)-lactonic acid (II)[2,6]. This key degradation product was assigned the absolute configuration 4S, 6R by Djerassi and co-workers[7] and 2S, 3R by Bergel'son and Batrakov[8], and corresponding stereochemical assignments were then made in the parent macrolides[7,8]. We show here that the 2S, 3R assignments[8] in the acid (II), and the resulting assignments[8] in the antibiotics themselves, should be reversed.

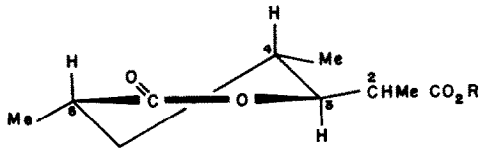


I II

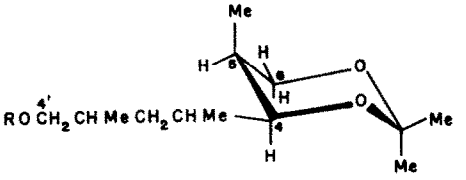
The pmr spectrum (in $CDCl_3$) of the natural lactonic acid (II) showed H_3 as a double doublet (J 2.3, 10.0 Hz) centred at τ 5.45, and a double quartet (J_d 2.3, J_q 7.5 Hz) at τ 7.27, which was confirmed as H_2 by irradiation at τ 5.45 when it collapsed to a quartet (J 7.5 Hz).

* Part XII, D.G. Manwaring, R.W. Rickards and B.T. Golding, submitted for publication.

Irradiation of H_2 collapsed the H_3 signal to a doublet (J 10.0 Hz) and a $CHC\underline{H}_3$ doublet at τ 8.78 (J 7.5 Hz) to a singlet. Thus $J_{3,4}$ must be 10.0 Hz, whilst $J_{2,3}$ must be 2.3 Hz. Similar pmdr results were obtained for the lactonic acid methyl ester, in which H_3 resonated as a double doublet at τ 5.50 with $J_{3,4}$ 10.0 Hz and $J_{2,3}$ 2.3 Hz, and H_2 as a double quartet, τ 7.30 (J_d 2.3, J_q 7.0 Hz). The magnitude of $J_{3,4}$ in these compounds necessitates[9] that these vicinal protons are anti-periplanar[10], and in conjunction with the previous 4S assignment[7] leads to the S configuration for C-3. The most likely conformation for the lactones is the half-chair form[11] (III; R = H or Me), although a half-boat form[11] is not excluded on pmr grounds.



III



IV

In order to relate the stereochemistry of C-2 to C-3 in the acid (III; R = H), the ester (III; R = Me) was reduced with lithium aluminium hydride to the triol[8], which with acetone and p-toluenesulphonic acid gave an hydroxyketal[8]. The 1,3-dioxan structure (IV; R = H) of this ketal follows from major mass spectroscopic fragmentations of the acetyl derivative (IV; R = MeCO) to give m/e 257 and 129, representing $(M - Me)^+$ and $(M - CHMeCH_2CHMeCH_2OCOMe)^+$ ions.

Pmr spectra of the acetylated 1,3-dioxan (IV; R = MeCO) showed resolved absorption due to five protons between τ 5.7 - 6.8, which could be interpreted with the aid of double irradiation and solvent shifts. The 4'-methylene protons appeared (in C_6D_6) at lowest field as the AB portion of an ABX system, double doublets too close in chemical shift for first order analysis. Three further double doublets centred at τ 6.25 (J 11.5, 2.5 Hz), 6.60 (J 11.5, 1.5 Hz) and 6.81 (J 8.9, 2.3 Hz) represent respectively the two mutually-coupled C-6 methylene protons * and the C-4 methine proton of the 1,3-dioxan ring. Irradiation at the H_5 frequency (τ 8.82) causes collapse of all three resonances to simple doublets with loss of the smaller coupling in each case. It follows from the Karplus dihedral angle relationship[9], coupled with the fact

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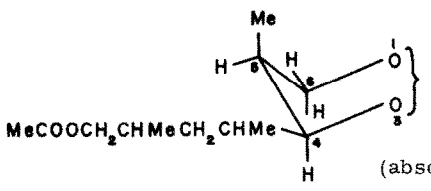
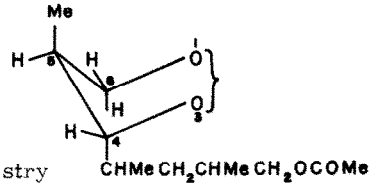
* These protons form the AB portion of an ABX system, the first order analysis of which was validated by an ABX computation of line positions and intensities.

that the system C-4,5,6 is part of a 6-membered ring, that H_5 is syn-clinal[10] to both H_6 protons and also to H_4. Two partial approximate conformations (V) and (VI) of the dioxan ring result. (VI) with the C-2 gem-dimethyl group added would involve severe axial-type interactions[12,13] and is not a possible preferred conformation. (V) remains, from which it follows that H_4 and H_5 are cis-related, and that the absolute configuration of C-5 is S.

These conclusions are valid regardless of the relative position of C-2, i.e., regardless of the overall conformation of the 1,3-dioxan ring. However, of the various conformations possible, the chair form (IV) is likely to be preferred, since boat and skew-boat forms will be destabilised by 2,5- and 2,4-alkyl-alkyl interactions[12,13]. This chair conformation (IV) and the embodied relative configurational assignments at C-4 and C-5 are confirmed by published chemical shift[14] and coupling constant[12,14] data, which also permit assignment of the τ 6.25 and 6.60 resonances to the equatorial and axial protons respectively at C-6. Thus in a series of substituted 1,3-dioxans, H_{4eq} and H_{6eq} resonated in the range τ 5.86 - 6.24, H_{4ax} and H_{6ax} at higher field between τ 6.44 - 6.96, whilst H_{5eq} resonated at τ 8.80 - 8.81 with H_{5ax} to lower field τ 7.97 - 8.09. $J_{4ax,5eq(6ax,5eq)}$ ranged between 2.5 - 4.4 Hz, $J_{4eq,5eq(6eq,5eq)}$ 1.2 - 1.9 Hz, $J_{4eq,5ax(6eq,5ax)}$ 3.3 - 6.6 Hz, $J_{4ax,5ax(6ax,5ax)}$ 9.0 - 13 Hz, and $J_{6eq,6ax}$ 10.1 - 11.3 Hz.



(absolute stereochemistry not implied)



V VI

The complete absolute stereochemistry of the natural lactonic acid (II) can now be designated as 2R, 3S, 4S[7], 6R[7], thus reversing Bergel'son and Batrakov's assignments*[8] at C-2 and C-3. Extension of these assignments to the parent antibiotics defines the partial absolute configuration of methymycin[2] and neomethymycin[3] as 2R, 3S, 4S[7], 6R[7], and of narbomycin[4] and picromycin[5] as 4R, 5S, 6S[7,5], 8R[7,5]. Allowing for the revision[5] of picromycin's structure, these conclusions are in complete agreement with the predictions of Celmer's

* These authors have apparently proven the relative stereochemistry of a racemic diastereoisomer of the natural acid (II). Their error probably stems from an incorrect identification, reportedly[15] based only on infrared spectra, of this diastereoisomer as the racemate of the natural acid.

configurational model[16] for macrolide antibiotics.

Acknowledgements: We thank Mr C. Arandjelovic for pmr spectra, and Dr R. Bramley for helpful discussion.

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