Tetrahedron Letters No.30, pp. 3567-3571, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF LUCENSOMYCIN. PART II

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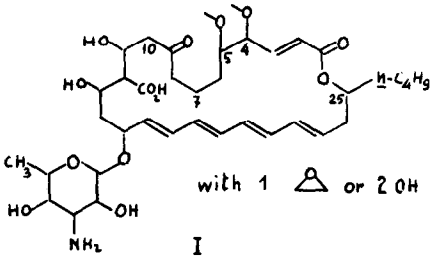
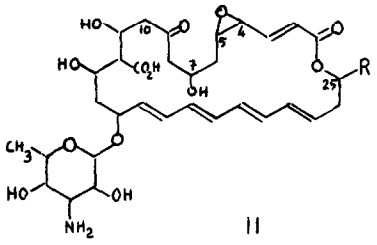
(Received 23 May 1966)

In the preceding paper (1) we developed the partial structure (I) for the macrolide antibiotic lucensomycin from Streptomyces lucensis. A close similarity was apparent between lucensomycin and the structure suggested by Ceder and co-workers (2) for pimaricin, a metabolite of S. natalensis. Apart from the definitive placement of some minor structural features, lucensomycin appeared to be a higher homologue of pimaricin in which a n-butyl group replaced the methyl group present at $C_{(25)}$ in the latter.



I



II

Mass spectrometry of trimethylsilyl* derivatives, a procedure developed by two of us (3) for the determination of mo-

* The abbreviation TMS will be used for trimethylsilyl.

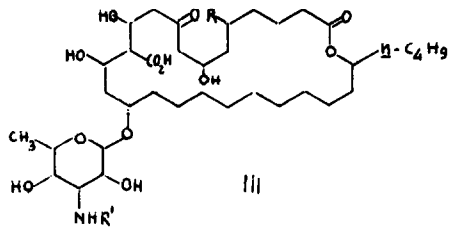
lecular formulae of polyhydroxylic compounds of high molecular weight, has recently (5) necessitated revision of the molecular formula of pimaricin from $C_{33}H_{47}NO_{14}$ (2) to $C_{33}H_{47}NO_{13}$, with a corresponding alteration in the structural formula to (II, R = CH_3). At this stage of the lucensomycin work, we determined the mass spectra of some TMS derivatives of lucensomycin for comparison with the corresponding pimaricin spectra. N-chloroacetyllucensomycin and N-acetyldodecahydrolucensomycin (in which the epoxide ring has been opened by hydrogenolysis) afforded TMS derivatives, the mass spectra of which indicated molecular formulae $C_{56}H_{102}ClNO_{14}Si_6$ (M^+ 1215) and $C_{59}H_{123}NO_{14}Si_7$ (M^+ 1265) respectively. These represent penta- and hexa-TMS ethers of N-acyl TMS esters, and necessitate that lucensomycin itself has the molecular formula $C_{36}H_{53}NO_{13}$, containing only five hydroxyl groups. The inaccuracy of analytical data (4) from which the previously accepted $C_{36}H_{53}NO_{14}$ formula was calculated is probably due to solvation of the macrolide crystals (*cf.* 3,5).

With this revision of the molecular formula of lucensomycin, it is now necessary to accomodate only one additional hydroxyl group together with the epoxide in the partial structure (I). Moreover, the close similarity of fragmentation patterns present in the above-mentioned spectra to those of TMS-N-acetyl derivatives of pimaricin and dodecahydropimaricin indicated that, apart from possible stereochemical differences, lucensomycin is the *n*-butyl homologue of the revised structure (II: R = CH_3) for pimaricin. Together with the additional chemical evidence summarized below, these facts permit us to assign to lucensomycin the structure (II: R = *n*-C_4H_9). Biogenetically lucensomycin carries an extra propionate unit in the aglycone compared to pimaricin.

Retroaldolisation of lucensomycin in the presence of hot

alkali afforded, together with the C_{17} pentaenal described previously (1,4) small amounts of acetone (chracterised by gas-liquid chromatography and isolation of the 2,4-dinitrophenylhydrazone). This eliminates the possibility of oxygenation at $C_{(8)}$ or $C_{(10)}$, establishes the position of the remaining hydroxyl group at $C_{(7)}$, and confirms the postulated (1,4) location of the epoxide function at $C_{(4)}$-$C_{(5)}$ in (II : R = n-C_4H_9).

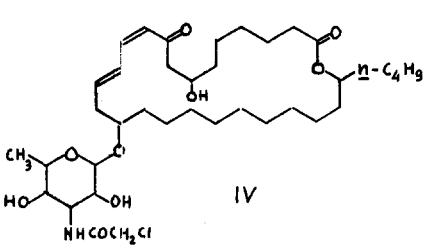
The absence of acyloin or vicinal diol groupings in the lucensomycin aglycone is further demonstrated by Lemieux oxidation of dodecahydrolucensomycin (III : R = OH; R' = H) with periodate/permanganate (6), which by demolition of the mycosamine moiety yields the corresponding dodecahydro-aglycone. This latter product was characterised by the mass spectrometric fragmentation pattern of its methyl ester. Although no molecular ion was observable at the required m/e 588, successive dehydrations related by metastable peaks gave rise to the intense ions at m/e 570, 552, 534 and 516, whilst a corresponding ketene series (formed by the elimination of water and methanol) occurred at m/e 538,520, 502, 484 and 466. In confirmation of this result, N-acetyldodecahydrolucensomycin (III : R = OH; R' = Ac) in which the susceptible free amino function is protected, resists similar oxidation. Characterisation of the unchanged compound (III : R = OH; R' = Ac)



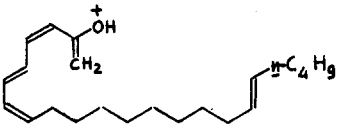
III

was effected by the mass spectrum of its fully-acetylated methyl ester. Here again the molecular ion at m/e 1027 was lacking, but all the principal fragment ions and related metastable ions were those to be expected from this derivative.

Mild acid treatment of N-chloroacetyldodecahydrolucensomycin gave, in low yield, a dienone (λ_{max} 282 mμ, ε_{max} 26300), which, from its spectroscopic properties and mode of formation is clearly the higher homologue (IV) of the corresponding product (5)



IV



V

from pimaricin (II : R = CH_3). Trimethylsilylation afforded a TMS derivative the mass spectrum of which showed a clear molecular ion at m/e 915, corresponding to $C_{46}H_{86}ClNO_9Si_3$. The free dienone should thus be $C_{37}H_{62}ClNO_9$, and whilst its mass spectrum does not show a molecular ion at m/e 699 (illustrating the advantage of TMS derivatives), this formula is confirmed by fragment ions at m/e 460 and 442 corresponding to the elimination of N-chloroacetylmycosamine both alone and together with water. Double McLafferty rearrangement(7) of the fragment of m/e 460 affords the structurally significant, intense ion (V) (Found : m/e 316.2777; $C_{22}H_{36}O$ requires m/e 316.2766). This dienone (IV), as with that from pimaricin, arises by acidic dehydration and decarboxylation not of N-chloroacetyldodecahydrolucensomycin itself (III : R = OH; R' = $COCH_2Cl$), but rather from an impurity, the desoxy-com-

pound (III : R = H; R' = CH_2Cl)probably formed by complete hydrogenolysis of the conjugate epoxide (cf.5). Its structure (IV) provides independent confirmation of the lucensomycin structure (II : R = n-C_4H_9), in particular of the positions of the epoxide and the mycosaminide linkage.

Acknowledgements.We are indebted to Società Farmitalia, Milano, for the generous supply of lucensomycin, and to the S. R. C. for a Research Studentship (to B. T. Golding), and we thank Miss R. Bernardi for gas chromatographs.

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