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MACROLIDE ANTIBIOTIC STUDIES. XVII.* CYCLIC HEMIKETAL STRUCTURES IN NYSTATIN, AMPHOTERICIN B, PIMARICIN AND LUCENSOMYCIN

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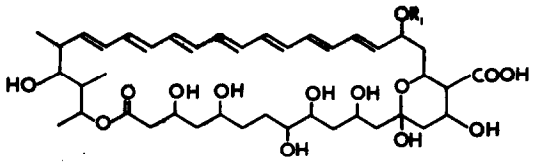
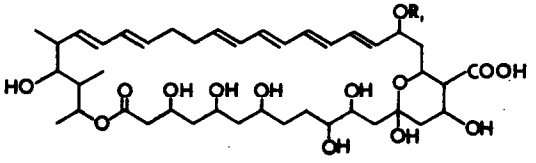
The ability of macrolide antibiotics of the polyene subgroup[1] to form complexes with sterols[2] gives rise to their extensive clinical usage as antifungal agents[3] and to their activity in control of hypercholesterolemia[4] and prostatic hypertrophy[5]. The formation of such complexes depends essentially on the presence of a macrocyclic lactone ring carrying opposed lipophilic polyene and hydrophilic polyol regions, other functionality merely modifying the biological activity[2]. The size[2] and conformation of the macrolide ring, however, will be important factors influencing the ease of formation, stoichiometry and stability of the sterol-polyene complex. The recent demonstration[6] by X-ray crystallography of the presence of a pyranoid internal hemiketal in the crystalline N-iodo-acetyl derivative of amphotericin B (I) is of interest in this regard in view of the restraints which it imposes on the macrolide ring. Spectroscopic studies now indicate that various polyene macrolides, which formally contain polyhydroxy-ketone functions, do not exist as such, but rather as cyclic hemiketals *in solution.*

Four antibiotics were studied: amphotericin B, known[6] to exist in crystalline form as the hemiketal (I); nystatin, to which we assigned[7] a structure subsequently confirmed by Borowski et al[8], and which we suggested[7] existed at least in crystalline form as the hemiketal (II) by analogy with amphotericin B; and pimaricin and its homologue lucensomycin, which were assigned[9,10] hydroxy-ketone structures and which we now believe exist as the hemiketals (III) and (IV). Since the hydroxy-ketone and cyclic hemiketal forms of these antibiotics are probably interconvertible upon the demand of a particular reagent, the formation of reaction products involving these centres does not constitute evidence for the preferred form of these

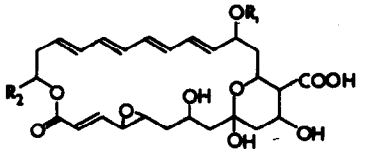
* Part XVI - Reference 7.



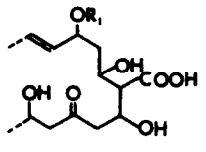
I



II



III; R_2 = Me
IV; R_2 = n-Bu



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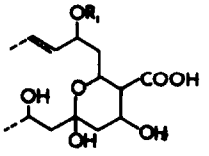
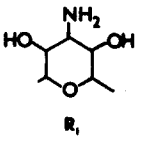


VI



antibiotics in neutral solution. Products arising from both components of such equilibria are known. Thus all four macrolides give three reactions characteristic of the presence of carbonyl functions, namely reduction by sodium borohydride, retro-aldol cleavage, and facile decarboxylation. On the other hand vigorous catalytic reduction in acetic acid of nystatin, pimaricin and lucensomycin yields tetrahydropyrans corresponding to the hemiketal forms (II), (III) and (IV) respectively. It should be noted, however, that the cyclic ethers in such products need not necessarily arise from hemiketals in the parent antibiotics, as seen by the four tetrahydrofurans formed[11] from nystatin, two of which arise from 1,4-diol functions. In particular, the production from amphotericin B of a tetrahydropyran fragment after extended degradation involving hydrobromic-acetic acid at one stage is not proof of the existence of a cyclic hemiketal in the antibiotic itself[12].

The common spectroscopic techniques for the detection of ketonic functions are inapplicable to these antibiotics due to their insolubility in appropriate neutral solvents, or do not give definitive answers because of their complexity. However, conversion of a ketone perturbed

by neighbouring asymmetry into a hemiketal or alcohol is accompanied by loss of the Cotton effect in its optical rotatory dispersion curve[13]. The ORD curves of the four antibiotics (Fig.1[14]) are unchanged after reduction with sodium borohydride to the dihydro-derivatives (completeness of reduction being confirmed in each case by the absence of retroaldolisation in mild alkali), implying that no significant contribution to the ORD of the parent antibiotics arises from ketone functions as such. Mild catalytic reduction of the antibiotics over

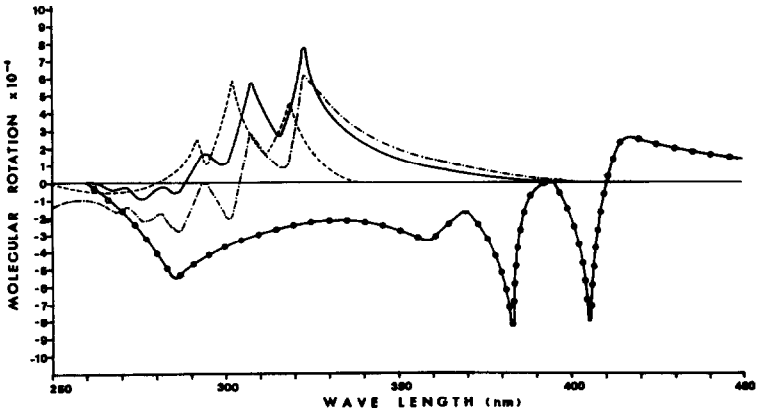


Fig.1 Optical rotatory dispersion curves (methanol solution) of nystatin(------), amphotericin B(——), pimaricin(——·——) and lucensomycin(—).

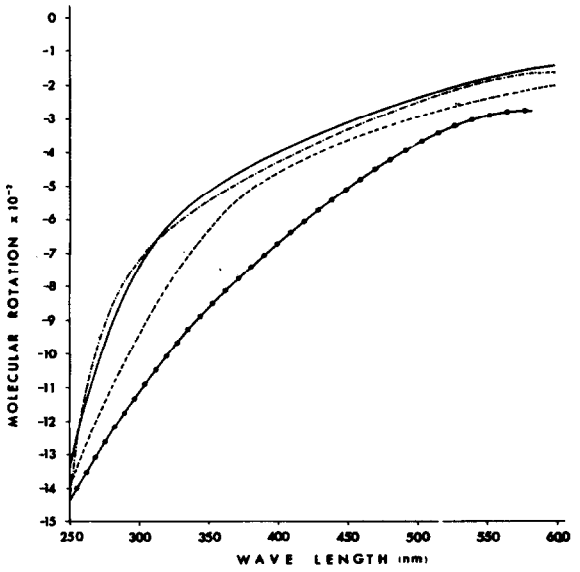


Fig.2 Optical rotatory dispersion curves (methanol solution) of perhydronystatin(------), perhydroamphotericin B(——), perhydro pimaricin(——·——) and perhydrolucensomycin(——).

palladium in methanol affords perhydro-derivatives in which multiple Cotton effects due to the polyene chromophores are no longer present. All four perhydro-derivatives show plain dispersion curves in the accessible ultraviolet region (Fig.2).

We conclude that, in neutral hydroxylic solution at ambient temperatures, ketone functions in these antibiotics and their perhydro-derivatives are masked. This masking does not involve the carboxyl or amino functions, which are free. Its reversibility under basic conditions necessitates that hemiketalisation is involved rather than ketalisation. It is notable that these and related antibiotics (e.g. candidin, tetrins A and B) contain the formal structural segment (V), of which the pyranoid hemiketal (VI) will probably be the preferred form, as seen in crystalline amphotericin B (I). This is the only form likely in the cases of pimaricin (III) and lucensomycin (IV).

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