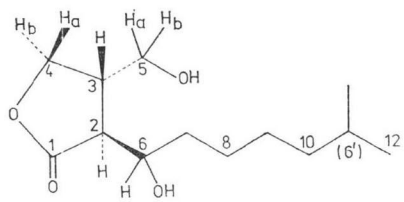
A NEW INDUCER OF ANTHRACYCLINE BIOSYNTHESIS FROM *STREPTOMYCES VIRIDOCHROMOGENES*

Sir:

It has been suggested that derivatives of butyrolactone play an important role in the cellular development of microorganisms[1~3]. This assumption has received support from the recent isolation of diastereomeric 4,5-dihydroxydecanoic acid-4-lactones, inducers of the formation of both spores and anthracycline antibiotics in blocked mutants of *Streptomyces griseus*[4]. By the use of conventional screening techniques[5], we have found that several taxonomically different Streptomycetes can produce substances which affect the indicator strains in a similar manner. To learn more about the relationship between biological activity and the chemical nature of inducers, efforts have been directed towards the isolation of further representatives of these agents. We report a new derivative of butyrolactone obtained from culture liquids of *Streptomyces viridochromogenes*.

S. viridochromogenes ZIMET 43683 from the strain collection of the Central Institute of Microbiology, Jena, was propagated and subsequently cultivated under aerobic conditions in a 400-liter fermentor for 96 hours as described[4]. The culture broth was extracted with 0.2 vol. of butyl acetate and chromatographed, first on a cellulose column (H_2O), then on preparative TLC sheets (Silufol; benzene - ether, 1: 1, $CHCl_3$ - MeOH, 95: 5, v/v) to yield 15 mg of the pure oily 2 - (6′ - methylheptanolyl) - 3 - hydroxymethyl - 4 - butanolide (**1**). IR and ^1H and ^{13}C NMR spectral data showed the purity of the product to be not less than 95%. Rf values (Silufol): 0.25 ($CHCl_3$ - MeOH, 95: 5, v/v); 0.08 (benzene - ether, 1: 1, v/v). Its UV spectrum (Specord UV/Vis, EtOH) shows an absorption maximum at 215 nm (ε 120) and the IR spectrum (Nicolet 7000 ET IR, $CDCl_3$ soln.) contains absorption peaks for a saturated five-membered γ-lactone (1767, 1172 cm^{-1}), and one primary (3625, 1036 cm^{-1}) and one intramolecularly H-bonded secondary (3440, 1080 cm^{-1}) hydroxyl function. From its mass spectrum (JEOL JMS-D 100, 75 eV, 328 K), product **1** has the elemental composition $C_{13}H_{24}O_4$ (*m/z*: 226.1580 [$M^+ - H_2O$; 226.1569 calcd. for $C_{13}H_{22}O_3$)]. The constitution and relative stereochemistry shown in formula **1** were inferred from the 200 MHz ^1H NMR (Bruker WP 200/SY) spectra (δ^{CDCl_3} ppm: H2 2.65, $J_{2,3}$=9.4, $J_{2,6}$=4.6; H3 2.76, $J_{3,4a}$=8.1, $J_{3,4b}$=8.6, $J_{3,5a}$=5.8, $J_{3,5b}$=6.2; H4a 4.42, $J_{4a,4b}$=−8.9; H4b 3.97; H5a 3.75, $J_{5a,5b}$=−10.6; H6 4.03, $J_{6,7}$=6.7; H7, H8, H9, H10 1.1~1.75; H11 1.49, $J_{11,12}$=6.8; H12, H13 0.87) and 25 MHz ^{13}C NMR (Varian XL-100/15) data (δ^{CDCl_3} ppm: C1 177.79 (s); C2 49.46 (d); C3 40.34 (d); C4 68.82 (t); C5 62.88 (t); C6 71.14 (d); C7 34.25 (t); C8 26.72 (t); C9 27.62 (t); C10 39.24 (t); C11 28.22 (d); C12 22.73 (q); C13 22.73 (q). Proton NMR data on saturated five-membered lactones[6] show that the vicinal $J_{2,3}$ coupling constant of 9.4 Hz corresponds to a *trans* relative orientation of the substituent groups at C2 and C3.



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(or the enantiomeric (2*R*,3*R*) form)

In bioassays by the paper disk method using surface cultures of the indicator strain *S. griseus* ZIMET 43682*, a minimum application of 75 ng (3×10^{-10} mole) induced visible signs of the formation of aerial mycelia and leukaemomycin. This was about half the amount of L-factors[4] and about 10 times higher than the amount of A-factor[1,2]** needed for the same effect. It suggests that the butyrolactone moiety and an aliphatic side chain with a polar substituent are of primary importance for the biological activity of these inducers, at least with strain ZIMET 43682.

Compound **1** has been obtained synthetically by ONOPRIENKO *et al. via* reduction of racemic A-factor[7]. These authors reported a nearly complete lack of biological activity. The apparent contradiction with observations described in the present communication may be attributed to differences in the indicator strains used.

* Identical with JA 5142/86[4,5].

** According to its 200 MHz ^1H NMR spectrum, a mixture of 2,3 *cis* and *trans* isomers.

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