The Stereochemistry of Olivomycins

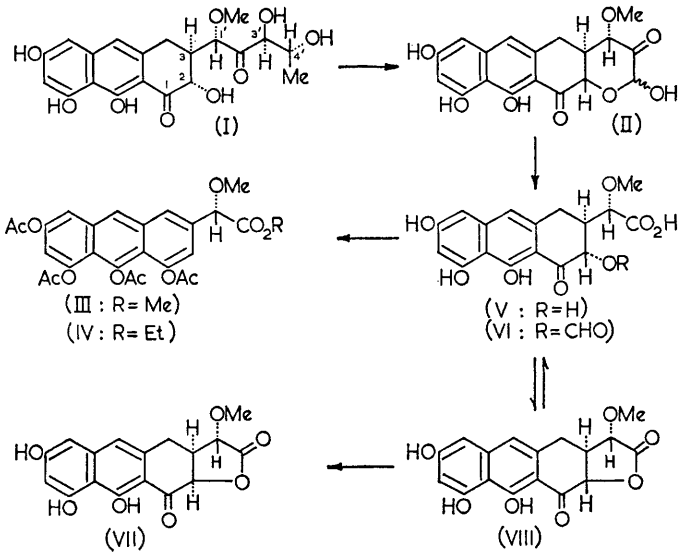
By G. P. BAKHAEVA, YU. A. BERLIN, O. A. CHUPRUNOVA, M. N. KOLOSOV, G. YU. PECK, L. A. PIOTROVICH, M. M. SHEMYAKIN, and I. V. VASINA

(*Institute for Chemistry of Natural Products, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.*)

RECENTLY we have reported the structure of the cancerostatic antibiotics, olivomycins, from *Streptomyces olivoreticuli*.[1] We now show that the absolute configuration of the olivomycin aglycone, olivin, may be depicted by (I), thereby completely elucidating the stereochemistry of these antibiotics.

On oxidation by periodate of olivin under strictly controlled conditions, it was converted *via* the hemiacetal (II) into 2-*O*-formylolivinic acid (VI) (m.p. 218—220°, from tetrahydrofuran; $[\alpha]_D^{20}$ −108°, *c*, 1 in EtOH) easily hydrolysable to olivinic acid (V) (m.p. 144—147°, from MeCN; $[\alpha]_D^{20}$ +16°, *c*, 1 in EtOH). Treatment of the latter with carbodiimides causes its dehydration to olivinolide (VIII) (decomp. 214—215°, from dioxan; $[\alpha]_D^{23}$ −148°, *c*, 0·3 in methylcellosolve; $\nu_{CO}^{(Nujol)}$ 1793 cm.$^{-1}$) which in the presence of bases or on heating is quantitatively isomerized into epi-olivinolide (VII) (m.p. 215—218°, from EtOH; $[\alpha]_D^{22}$ −247°, *c*, 0·3 in methylcellosolve; $\nu_{CO}^{(Nujol)}$ 1782 cm.$^{-1}$). The n.m.r. spectra of these lactones display doublets for the C_2-protons in the region of $\delta = 5$ p.p.m. with $J = 12$ and 6 c./sec., respectively, whereas $H_{1'}$ of both compounds resonates as a doublet at 4—4·5 p.p.m. with $J \sim 10$ c./sec. These data, as well as comparison with the n.m.r. spectrum of *trans-threo*-2-hydroxycyclohexyl-*NN*-dimethylglycine lactone,[2] proves the *all-trans* position of the protons at C_2, C_3, and $C_{1'}$ in olivinolide (VIII) and hence, the *trans,threo* configuration of olivinic acid (V).

Heating methyl olivinate (m.p. 215—217°, from EtOH; $[\alpha]_D^{24}$ −10°, *c*, 1 in EtOH) with acetic anhydride converts it with high yield into the anthracene derivative (III) (m.p. 222—223°, from EtOH; $[\alpha]_D^{20}$ +84°, *c*, 1 in $CHCl_3$) exhibiting the characteristic u.v. and n.m.r. spectra. A comparison of the rotatory dispersion of this compound and the analogously prepared ethyl ester (IV) (m.p. 254—257°, from EtOH; $[\alpha]_D^{23}$ +12°, *c*, 1 in $CHCl_3$) with the rotatory dispersion of the corresponding D-*O*-methylmandelic esters showed the former compounds to be of the L-configuration. Therefore olivinic acid (V) and consequently olivin (I) has a 2*S*,3*R*,1′*S* configuration. As for the remaining two asymmetric centres of olivin



($C_{3'}$ and $C_{4'}$) their configuration follows from the formation of *threo*-2,3-dihydroxybutyric acid on $CF_3{\cdot}CO_3H$ oxidation of hexa-acetylolivin and the formation of D-acetyl-lactic acid on periodate–permanganate oxidation of 2,6,8,9,4′-penta-acetyl-olivin ($[\alpha]_D^{20}$ +33°, *c*, 1 in C_6H_6). Hence olivin has the 2*S*,3*R*,1′*S*,3′*S*,4′*R* configuration (I).[3]

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[1] Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, and M. M. Shemyakin, *Tetrahedron Letters*, 1966, 1643.
[2] M. N. Kolosov and Yu. A. Berlin, *Zhur. obshchei. Khim.*, 1962, **32**, 2893.
[3] According to a private communication by Prof. K. Nakanishi, the chromomycin aglycone, chromomycinone, has a similar configuration.