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THE STEREOCHEMISTRY OF ANTIBIOTICS OF THE AUREOLIC ACID GROUP

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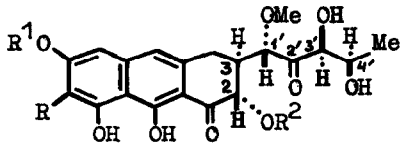
AUREOLIC acid (mithramycin, LA-7017), chromomycins (aburamycins) and olivomycins (NSC A-649) comprise a single group of anti-tumour antibiotics of the general formula (Ia) (1-4). Their aglycones, chromomycinone and olivin, structurally elucidated by Japanese chemists (5) and by us (6), respectively, were ascribed different absolute configuration: olivin was formulated as (Ib) (7), while chromomycinone as 2,3,1′-enantio-(Ic) (8,9). Since the difference was at variance with the biogenetic relationship of the antibiotics, we correlated the configurations of olivin and chromomycinone and by stepwise degradation of the former to a derivative of D-(+)-tartaric acid chemically proved the absolute configuration S for the $C_{1'}$ asymmetric centre of the two aglycones.



(I)

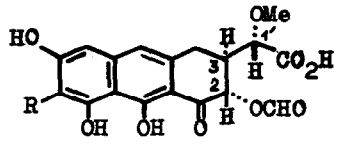
(Ia): R^1 and R^2 = carbohydrate chains
R = H or Me

(Ib): R = R^1 = R^2 = H

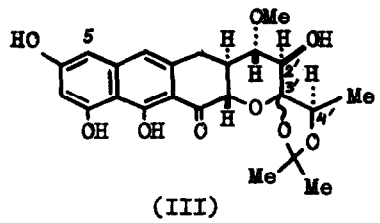
(Ic): R = Me, R^1 = R^2 = H

Periodate oxidation of chromomycinone (Ic) yielded formylchromomycinonic acid (IIb) (m.p. 220-221°, from acetonitrile; $[\alpha]_D^{20}$ +72°, in ethanol).

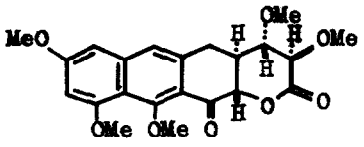
The ORD curves of (IIb) and the previously reported formylolivinic acid (IIa) (10) and of the two aglycones (as peracetates) in the range 280-600 nm proved to be quite similar, from which follows the identity of both the relative and the absolute configurations of olivin and chromomycinone.



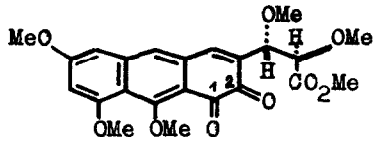
(IIa): R = H
(IIb): R = Me



(III)



(IV)



(V)

Similar to chromomycinone (11), 3′-hydroxy-2′-ketone olivin was isomerized by 0.1 N KOH to the 2′-hydroxy-3′-ketone, isoolivin, which yielded the 3′,4′-isopropylidene derivative (III) (m.p. 214-215° dec., from methanol; $[\alpha]_D^{25}$ +45°, in ethanol). When the reaction was carried out in D_2O, only $H_{2'}$ and H_5 were substituted by deuterium, as shown by the NMR and mass spectra; hence the $C_{1'}$ asymmetric centre was not affected in the isomerization. Compound (III) was permethylated by MeI + NaH in dimethylsulfoxide and the product after hydrolysis by 0.2 N HCl and oxidation by $Pb(OAc)_4$ yielded the lactone (IV) (m.p. 206-207° dec., from ethanol; $[\alpha]_D^{25}$ +29°, in benzene). This lactone on methanolysis with 5% methanolic HCl and subsequent dehydrogenation by Me_2SO + Ac_2O gave the 1,2-quinone (V) (m.p. 204-205°, from ethanol; $[\alpha]_D^{25}$ +108°, in acetone). Permanganate oxidation of the quinone afforded D-(+)-tartaric acid dimethyl ether ($[\alpha]_D^{25}$ +69°, in acetone), identical to an authentic sample.

Thus by direct chemical evidence the 2S,3R,1'S,3'S,4'R absolute configuration (I) has been unequivocally substantiated for all antibiotics of the aureolic acid group.

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