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THE STRUCTURE OF AUREOLIC ACID (MITHRAMYCIN)

G.P.Bakhaeva, Yu.A.Berlin, E.F.Boldyreva, O.A.Chuprunova,
M.N.Kolosov, V.S.Soifer, T.E.Vasiljeva and I.V.Yartseva

Institute for Chemistry of Natural Products
USSR Academy of Sciences, Moscow, USSR

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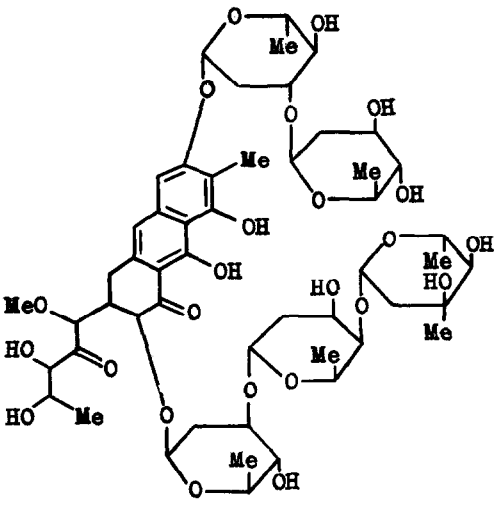
AUREOLIC acid from Streptomyces sp. (1), the parent substance of an important group of antitumour antibiotics, had recently been shown (2) to be identical with antibiotics LA-7017 (3) and mithramycin (4). We have now found it to possess structure I.



I

The antibiotic is a glycoside $C_{52}H_{76}O_{24}$ (m.p. 180-183°, from Me_2CO; $[\alpha]_D^{20}$ -51°, c 0.4 in EtOH) that on acid hydrolysis yielded chromomycinone (V), D-mycarose (II), D-olivose (III) and D-oliose (Iv) in the ratio 1:1:3:1,

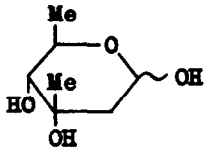
the product being identified by direct comparison with the aglycone V of the chromomycins (5) and with the sugars L-II, D-III and D-IV isolated from magnamycin (6), olivomycin A (7) and olivomycin C (8), respectively.

Aureolic acid greatly diminishes the pH of boric acid solutions (ΔpH 2.5), indicating that in the antibiotic the peri-dihydroxynaphthalene group of chromomycinone is free (cf. (7)). On periodate oxidation of aureolic acid under conditions not affecting the glycoside bonds degradation of the terminal sugars and the aglycone side chain takes place with liberation of one mole each of HCO_2H and AcH; hence the 3'-OH and 4'-OH hydroxyls of the aglycone moiety also must be free. The oxidation product only retains intact one oliose and two olivose residues, the aglycone having become chromomycinonic acid (VI) obtainable from chromomycinone (V) by periodate oxidation (cf.(9)). On acid degradation of the benzoate of the antibiotic (by methanolic HCl, then AcOH aq.) oliose (IV) was isolated as the 3-benzoate and olivose (III) as a mixture of the 3,4-dibenzoate and the 4-monobenzoate. Therefore aureolic acid contains two unbranched carbohydrate chains attached to the aglycone through the 2-OH and 6-OH hydroxyls and terminated by mycarose (II) and olivose (III), the oliose residue being glycosided *via* the 4-OH and two of the olivose residues *via* the 3-OH hydroxyls.

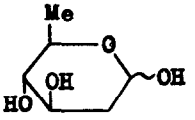
The periodate oxidation product was reduced by $NaBH_4$, subsequent mild hydrolysis by 0.1 N HCl yielding oliosyl-olivosyl-olivosyl-chromomycinonic acid (VII). The latter subjected to benzoylation followed by acid degradation (similarly to the benzoate of the antibiotic) afforded the 3,4-dibenzoates of olivose and oliose and the 3-monobenzoate of olivose. Partial hydrolysis of aureolic acid yielded two isomeric monosides, namely 2- and 6-olivosyl-chromomycinones, and a mycarose-free tetroside in which the oliose residue is readily destroyed by $NaIO_4$. These results lead to mycarosyl-(1$\rightarrow$4)oliosyl(1$\rightarrow$3)olivosyl and olivosyl(1$\rightarrow$3)olivosyl structures for the carbohydrate chains.

To locate the chains the antibiotic was treated with potassium nitrosodisulfonate in acetic acid solution. The reaction resulted in the oxida-

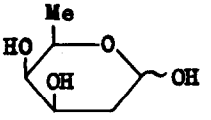
tion of the aglycone moiety to a quinone and removal of the olivosyl-olivosyl chain, which shows it to be at the 6 position, leaving the 2 position for the trisaccharide chain.



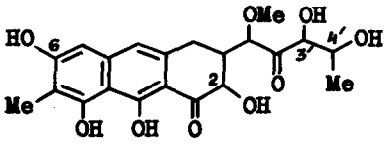
II



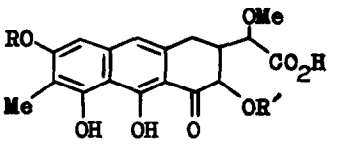
III



IV



V



VI: R = R′= H
VII: R = III(1→),
R′= IV(1→3)III(1→)

Finally, the molecular rotation of aureolic acid and its partial hydrolysis products treated according to Klyne's rule indicated that of the five sugar residues present in the antibiotic oliose is of the α-configuration, while the rest are of the β-configuration.

Thus, aureolic acid is 2-[β-mycarosyl(1→4)α-oliosyl(1→3)β-olivosyl]-6-[β-olivosyl(1→3)β-olivosyl]-chromomycinone (I).

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