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THE STRUCTURE OF THE OLIVOMYCIN-CHROMOMYCIN ANTIBIOTICS (1)

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THE mixture of antibiotics produced by Streptomyces olivoreticuli is separated into the individual components: olivomycins A, B, C and D by thin layer chromatography on silica gel (in solvent system benzene-acetone 1:1 R_A 1.00, 0.83, 0.61 and 0.51, respectively). Earlier the first of these antibiotics under the names "olivomycin" and "variant I" was characterized chemically (2,3) and biologically (4), while olivomycins B and C as a mixture were described under the name "variant II" (2); perhaps olivomycin D is what was called "variant III" (2). In a study of these antibiotics we have shown that they are all structurally similar both to each other and to the chromomycins from Streptomyces griseus, investigated by Japanese chemists (5).

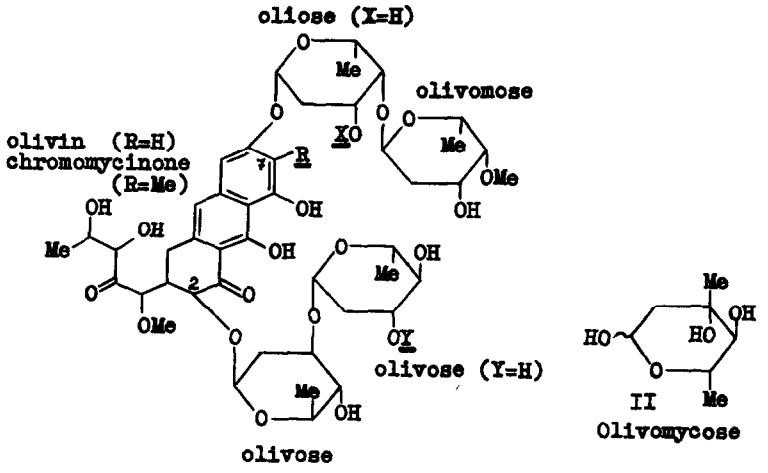
Olivomycin A (earlier simply olivomycin), $[\alpha]_D^{20}$ -36° (c 0.5 in EtOH), λ_{max}^{EtOH} mμ (lg ε) 228 (4.39), 277 (4.67), 308 (shoulder), 318 (3.81), 330 (shoulder), 406 (4.05). As shown in the previous communication (6) this antibiotic has the structure Ia ($C_{58}H_{84}O_{26}$).

Olivomycin B, $[\alpha]_D^{20}$ -28° (c 1 in EtOH), λ_{max}^{EtOH} mμ (lg ε) 228 (4.34), 276 (4.64), 308 (shoulder), 318 (3.78), 330 (shoulder), 406 (4.02). Hydrolysis of this antibiotic with 50% acetic acid yields almost the same products and in the same proportions as hydrolysis of olivomycin A; the only difference being in that the olivomycin B hydrolysate contains olivomycose (II) as the 4-acetate (7), instead of as the 4-isobutyrate. Hence olivomycin B possesses the structure Ib ($C_{56}H_{80}O_{26}$).

Olivomycin C, $[\alpha]_D^{20}$ -17° (c 0.3 in EtOH), λ_{max}^{EtOH} mμ (lg ε) 228 (4.36), 277 (4.67), 308 (shoulder), 319 (3.87), 330 (shoulder), 406 (4.04). The hydrolysate of this antibiotic was perfectly similar to that of olivomycin A, excepting only that it contained oliose instead of its 3-acetyl derivative. The conclusion following therefrom that olivomycin C is deacetylolivomycin A was proved by acetylation with Ac_2O + Py to form the earlier described (6,9) olivomycin A acetate. Hence olivomycin C has the structure Ic ($C_{56}H_{82}O_{25}$).

Olivomycin D, $[\alpha]_D^{20}$ -25° (c 0.8 in EtOH), λ_{max}^{EtOH} mμ (lg ε) 227 (4.30), 275 (4.70), 308 (shoulder), 319 (3.97), 330 (shoulder), 406 (4.04). This antibiotic has been shown to possess the structure Id ($C_{47}H_{66}O_{22}$) by direct comparison with the corresponding partial hydrolysis product of olivomycin A (6).

As for chromomycins, the Japanese workers in the years 1964-1965 have successively proposed two different structures for the major antibiotic of this group, chromomycin A_3 (10, 11), and have recently proposed still another formula (5), which differs from If in the absence of one of the two olivose



OLIVOMYCINS: R = H

(Ia) Olivomycin A: X = Ac, Y = α-4-isobutyrylolivomycosyl

(Ib) Olivomycin B: X = Ac, Y = α-4-acetylolivomycosyl

(Ic) Olivomycin C: X = H, Y = α-4-isobutyrylolivomycosyl

(Id) Olivomycin D: X = Ac, Y = H

CHROMOMYCINS: R = Me

(Ie) Chromomycin A_2: X = Ac, Y = α-4-isobutyrylolivomycosyl

(If) Chromomycin A_3: X = Ac, Y = α-4-acetylolivomycosyl

(Ig) Deacetylchromomycin A_3: X = Ac, Y = α-olivomycosyl

(Ih) Chromomycin A_4: X = Ac, Y = H

(or chromose C according to the Japanese nomenclature) residues at the C_2 of the aglycone. Owing to the high similarity in biological and chemical properties of the olivomycin and chromomycin antibiotics this formula appeared to us to be somewhat dubious and we repeated the hydrolysis of chromomycin A_3 by 50% AcOH (8). It was found that with respect to the sugars the hydrolysate of chromomycin A_3 is indistinguishable from that of olivomycin B, i.e. it contains two moles of olivose per mole of 4-acetylolivomycose, olivomose and 3-acetyloliose. This fact demonstrates the invalidity of the formulas proposed by the Japanese chemists and in conjunction with the earlier published data (5) points out to structures Ie ($C_{59}H_{86}O_{26}$), If ($C_{57}H_{82}O_{26}$) and Ih ($C_{48}H_{68}O_{22}$) for chromomycins A_2, A_3 and A_4, respectively, and to Ig ($C_{55}H_{80}O_{25}$) for deacetylchromomycin A_3.

It, therefore, follows that olivomycins and chromomycins comprise a single group of cancerostatic antibiotics of the general type I, the chromomycins being 7-methylolivomycins.

REFERENCES

1. Part V in the olivomycin series.
2. M.G.Brazhnikova, E.B.Kruglyak, I.N.Kovsharova, N.V.Konstantinova, V.V.Proshlyakova, Antibiotiki, 7, No.3, 34 (1962).
3. Yu.A.Berlin, S.E.Esipov, M.N.Kolosov, M.M.Shemyakin, M.G. Brazhnikova, Tetrahedron Letters, 1964, 1323.
4. I.A.Kunrat, Antibiotiki, 7, No.3, 44 (1962), and subsequent papers.

5. M.Miyamoto, Y.Kawamatsu, K.Kawashima, M.Shinohara, K.Nakanishi, Tetrahedron Letters, 1966, preprint. The authors express their acknowlegement to Prof. M.G.Brazhnikova for acquainting them with the preprint of this paper.
6. Yu.A.Berlin, S.E.Esipov, M.N.Kolosov, M.M.Shemyakin, Tetrahedron Letters, 1966 (in press).
7. It was found by direct comparison that olivomycose 4-acetate is identical with chromose B (8) obtained by hydrolysis of chromomycin A_3. We are greatly indebted to Prof. A.S.Khokhlov for a sample of chromomycin A_3.
8. M.Miyamoto, Y.Kawamatsu, M.Shinohara, K.Nakanishi, Y.Nakadaira, N.S.Bhacca, Tetrahedron Letters, 1964, 2371.
9. A.S.Mezentsev, E.B.Kruglyak, V.N.Borisova, G.B.Fedorova, M.G.Brazhnikova, Antibiotiki, 10, 410 (1965).
10. M.Miyamoto, K.Morita, Y.Kawamatsu, M.Sasai, A.Nohara, K.Tanaka, S.Tatsuoka, K.Nakanishi, Y.Nakadaira, N.S.Bhacca, Tetrahedron Letters, 1964, 2367.
11. K.Nakanishi, Communication at the NIAMD-LC Seminar, June 1, 1965, Bethesda, Md., USA.