The Structure of Chromocyclomycin

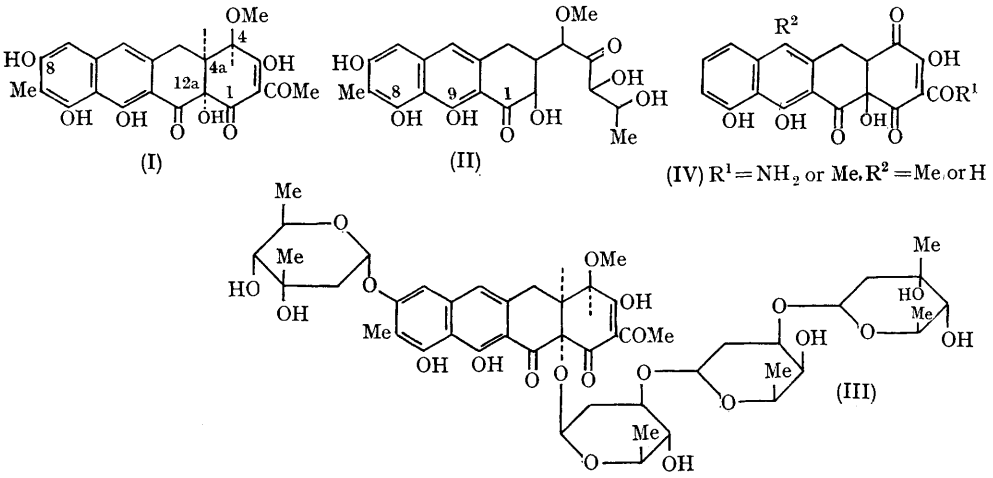
By YU. A. BERLIN, M. N. KOLOSOV,* I. V. VASINA, and I. V. YARTSEVA
(*Institute for Chemistry of Natural Products, USSR Academy of Sciences, Moscow*)

CHROMOCYCLOMYCIN, a new streptomycete metabolite recently isolated from *Streptomyces* LA-7017,[1] in addition to the antitumour antibiotic LA-7017,[2] has proved to be a glycoside $C_{48}H_{64}O_{21}$, m.p. 196—198° (from Me_2CO), $[\alpha]_D^{27}$ −180° (*c* 0·3 in EtOH), λ_{max} (EtOH) 229, 283, 322, 335, and 420 mμ (log ε 4·54, 4·74, 4·21, 4·13, and 4·02), yielding three sugars on hydrolysis with 50% acetic acid, 3-*C*-methyl-2,6-dideoxy-D-*ribo*-hexose (mycarose), 2,6-dideoxy-D-*arabino*-hexose (olivose, chromose C, canarose), and 2,6-dideoxy-D-*lyxo*-hexose (oliose, deacetylchromose D) in a 2 : 1 : 1 ratio. The aglycone, $C_{22}H_{20}O_9$, m.p. 226—228° (from MeCN), $[\alpha]_D^{27}$ − 415° (*c* 0·3 in EtOH), has been named chromocycline to emphasize its structural relationship to *chromo*mycinone (II)[3] and the tetra*cyclines*.[4]

The structure of the sugars had been elucidated previously.[5] The structure of chromocycline (I) was established on the basis of the following: chromocycline contains a methoxyl on a saturated C-atom, an aromatic methyl, a *C*-acetyl in a β-diketone grouping, two isolated aromatic protons, four phenolic or enolic hydroxyls, of which two are involved in chelate groupings, and an alcoholic hydroxyl, but no unconjugated carbonyls. Of two titratable groups (pK_a 4·8 and 6·8) the first resembles acetyldimedone in acidity, while the second is like the 1,8,9-oxodiphenolic grouping of chromomycinone (II). The mass spectrum of chromocycline indicates the presence of the tricyclic moiety of chromomycinone since, as with (II), the base peak in the higher mass range is due to the *m/e* 272 fragment, arising from cleavage of the 4*a*–4 and 12*a*–1 bonds. The u.v. spectrum of chromocycline indicates the presence of two chromophores, subtraction of the absorption of (II) from that of (I) giving a curve resembling the difference curve obtained by subtracting the absorption of the model 8,9-dihydroxy-10-methyl-1-oxo-1,2,3,4-tetrahydroanthracene from that of the appropriate anhydrotetracycline. The chromophores are separated by a tertiary alcohol group which undergoes hydrogenolysis on mild treatment with Zn + AcOH, the reaction resulting in a bathochromic shift of the long-wave absorption (λ_{max} 422 → 455 mμ).

Periodate oxidation of chromocyclomycin destroys both mycarose residues but does not affect the olivose or oliose residues. Partial hydrolysis of chromocyclomycin gives mycarosylchromocycline ($[\alpha]_D^{27}$ −235°, *c* 0·8 in EtOH), olivosylchromocycline ($[\alpha]_D^{27}$ −365°, *c* 0·8 in EtOH) and mycarosylolivosylchromocycline ($[\alpha]_D^{27}$ −230°, *c* 0·8 in EtOH), whereas complete hydrolysis of chromocyclomycin perbenzoate yields among other products 4-benzoylolivose and 4-benzoyloliose. It thus follows that in the chromocyclomycin molecule one of the aglycone hydroxyls is attached to a mycarose residue and another to a mycarosyl(1 → 3)oliosyl(1 → 3)olivosyl chain.

The acidity constants of chromocyclomycin are almost identical to those of chromocycline. Hence, both the *peri*-dihydroxyketone and acetyldimedone groups of the former must be free, so that it is the 8- and 12a-hydroxyls of chromocycline which are involved in the binding of the carbohydrate chain. The u.v. absorption of chromocycline and olivosylchromocycline but not of chromocyclomycin or mycarosylchromocycline undergoes a bathochromic shift upon basification. This means that in chromocyclomycin the mycarose residue blocks the 8-phenolic hydroxyl, whereas the trisaccharide chain is joined to the



(I) (II) (IV) $R^1 = NH_2$ or Me, R^2 = Me or H (III)

12a-OH. Independent evidence of the position of the sugars follows from the fact that hydrogenolysis of the trisaccharide chain on reduction of chromocyclomycin by Zn + NH_3(aq.) yields mycarosyl-12a-deoxychromocycline.

Calculation of the molecular rotations according to Klyne's rule indicates the α-configuration for the mycarose residue linked directly to chromocycline and the α,β,β or β,α,β configuration for the mycarosyl–oliosyl–olivosyl chain. In addition the available evidence permits chromocycline to be tentatively assigned a 4*R*,4a*S*,12a*S*-configuration (I). Hence, chromocyclomycin is formulated as (III).

Since compounds of type (IV) are biogenetic precursors of tetracyclines,[6] the structure of chromocycline implies a similarity in the biosynthetic pathways to these well known antibiotics and to the aglycone moiety of olivomycin–chromomycins.[7]

We thank Professor P. Sensi (Lepetit, Milan) for the sample of *Streptomyces* LA-7017.

(*Received, May 2nd,* 1968; *Com.* 544.)

[1] Yu. A. Berlin, O. A. Kiseleva, M. N. Kolosov, M. M. Shemyakin, V. S. Soifer, I. V. Vasina, I. V. Yartseva, and V. D. Kuznetsov, *Nature*, 1968, **218**, 193.

[2] P. Sensi, A. M. Greco, and H. Pagani, *Antibiotics a. Chemotherapy*, 1958, **8**, 241.

[3] M. Miyamoto, K. Morita, Y. Kawamatsu, S. Noguchi, R. Marumoto, K. Tanaka, S. Tatsuoka, K. Nakanishi, Y. Nakadaira, and N. S. Bhacca, *Tetrahedron Letters*, 1964, 2355.

[4] H. Muxfeldt and R. Bangert, *Fortschr. Chem. Org. Naturstoffe*, 1963, **21**, 80.

[5] B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc.* (*C*), 1966, 398; P. Studer, S. K. Pavanaram, C. R. Gavilanes, H. Linde, and K. Meyer, *Helv. Chim. Acta*, 1963, **46**, 23; Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, M. M. Shemyakin, and M. G. Brazhnikova, *Tetrahedron Letters*, 1964, 3513; M. Miyamoto, Y. Kawamatsu, M. Shinohara, K. Nakanishi, Y. Nakadaira, and N. S. Bhacca, *Tetrahedron Letters*, 1964, 2371.

[6] J. R. D. McCormick, "Biogenesis of Antibiotic Substances", Prague, 1965, p. 73.

[7] Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, and M. M. Shemyakin, *Tetrahedron Letters*, 1966, 1643; M. Miyamoto, Y. Kawamatsu, K. Kawashima, M. Shinohara, K. Tanaka, S. Tatsuoka, and K. Nakanishi, *Tetrahedron*, 1967, **23**, 421.