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BIOGENESIS OF MACROLIDES.[1] ORIGIN OF THE BRANCHED METHYL GROUPS IN CLADINOSE AND MYCAROSE

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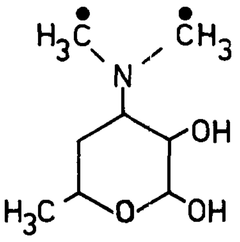
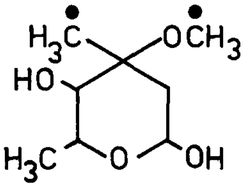
IN our investigation of the biogenesis of erythromycin[2] we had found that in an experiment with L-methionine-[methyl-^{14}C] the lactone ring was inactive, while desosamine (I)[3] contained about 1/3 and cladinose (II)[4] about 2/3 of the activity, even though II has only one O-methyl group while desosamine has a dimethylamino group. As one explanation for this result we assumed that methionine might supply not only the methoxyl group in II but also the C-methyl group at C-3. We now wish to report the experimental proof that the C-methyl groups at C-3 in cladinose and mycarose



I



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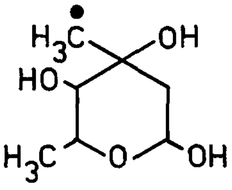

III

• denotes origin from the methyl group of methionine

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[1] Part III: H. Grisebach and H. Achenbach, Z. Naturf. In press.

[2] H. Grisebach, H. Achenbach and W. Hofheinz, Z. Naturf. 15b,560 (1960).

[3] E.H. Flynn, M.V. Sigal, Jr., P.F. Wiley and K. Gerzon, J.Amer. Chem. Soc. 76, 3121 (1954).

(III)[5] originate from the methyl group of methionine.

Fermentation of Streptomyces erythreus and Streptomyces halstedii in the presence of L-methionine-[methyl-^{14}C] yielded radioactive erythromycin and magnamycin (IV)[6] respectively. The distribution of the radioactivity is shown in Table 1.

Table 1

Compound	Per cent radioactivity
Erythromycin	100
Desosamine	40
Cladinose	60
Dimethylamine from desosamine	100 (of desosamine)
Acetic acid from Kuhn-Roth oxydation of cladinose	67 (of cladinose)
Carboxyl group of acetic acid	0.7
Magnamycin	100
Carimbose	79
Isovaleric acid	0
Acetic acid from Kuhn-Roth oxydation of carimbose	0.4
Acetic acid from Kuhn-Roth oxydation of magnamycin	24
Mycarose	23
Acetaldehyde from periodate oxydation of mycarose	0

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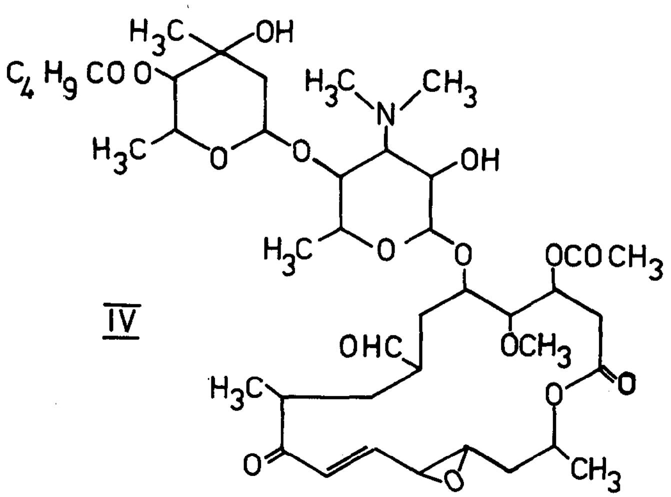
[4] P. F. Wiley and O. Weaver, J.Amer.Chem.Soc. 78, 808 (1956)

[5] P.P. Regna, F.A. Hochstein, R.L. Wagner, Jr. and R.B. Woodward, J.Amer.Chem.Soc. 75, 4625 (1953).

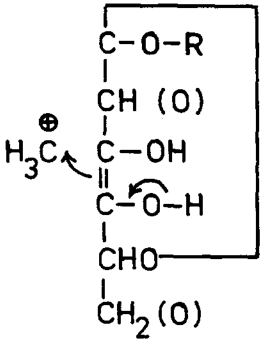
[6] R.B. Woodward, Angew. Chem. 69, 50 (1957).



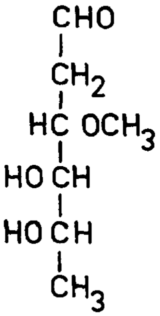
IV

In agreement with our previous results[2] cladinose contained 60 per cent and desosamine 40 per cent of the total activity in erythromycin. Sixty-seven per cent of the activity in cladinose was in the C-methyl groups, while the entire activity in desosamine was localized in the dimethylamino group. In the case of magnamycin no activity was found in the C-methyl groups of carimbose (magnamycin minus isovaleryl-mycaroside). The activity in carimbose is probably distributed between the N-dimethylamino group of mycaminose and the methoxyl group on the lactone ring; the branched methyl group at C-10 is derived from propionate.[1] The entire activity in mycarose was localized in the C-methyl groups. Periodate oxidation of III yielded acetaldehyde (C-5 and C-6) which was inactive, thus proving that only the methyl group at C-3 originated from methionine. This almost certainly applies to cladinose as well.

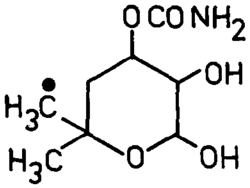
The selective methylation of the sugar carbon chain at C-3 seems reasonable only if it is assumed that it occurs at an intermediate stage in which C-3 is activated. A suitable activated intermediate would be, for instance, a uridinediphosphate derivative of V.



V



VI



VII

The origin of the unbranched carbon chain of cladinose and mycarose is currently being investigated in this laboratory. It seems plausible that these sugars are biogenetically very closely related to L-oleandrose (VI)[7] from oleandomycin and oleandrin. Possibly the steric configuration of II and III, as yet unknown, is the same as that of VI.

Birch et al.[8] have recently demonstrated that in the case of novobiose (VII) from novobiocin one of the two terminal C-methyl groups also originates from methionine.

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[7] H. Els, W.D. Celmer and K. Murai, J.Amer.Chem.Soc. 80, 3777 (1958).

[8] A.J. Birch, D.W. Cameron, P.W. Holloway and R.W. Rickards, Tetrahedron Letters No. 25, 26 (1960).