Biosynthesis of the Antiviral Antibiotic 11-Demethyltomaymycin by *Streptomyces Achromogenes*

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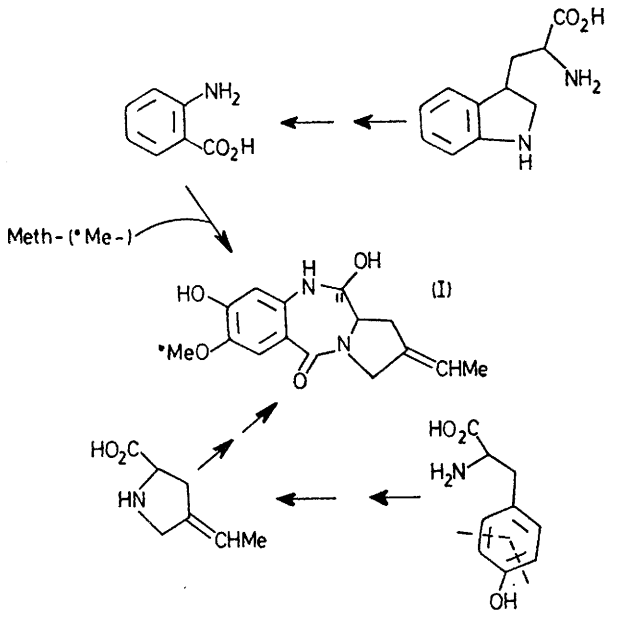
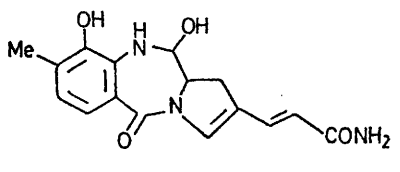
Summary The building blocks for 11-demethyltomaymycin have been established as tryptophan, tyrosine and a one carbon unit *via* methionine.

11-DEMETHYLTOMAYMYCIN (DMT) (I) is an antiviral antibiotic produced by *Streptomyces achromogenes* var *tomaymycetics*.[1] We now report the biogenetic origin of the non 5-methoxy 4-hydroxyanthranilic acid part of the antibiotic. The results show that DMT is derived from tryptophan, tyrosine and a one carbon unit *via* methionine. This is consistent with the biogenetic scheme shown in Scheme 1.



SCHEME 1

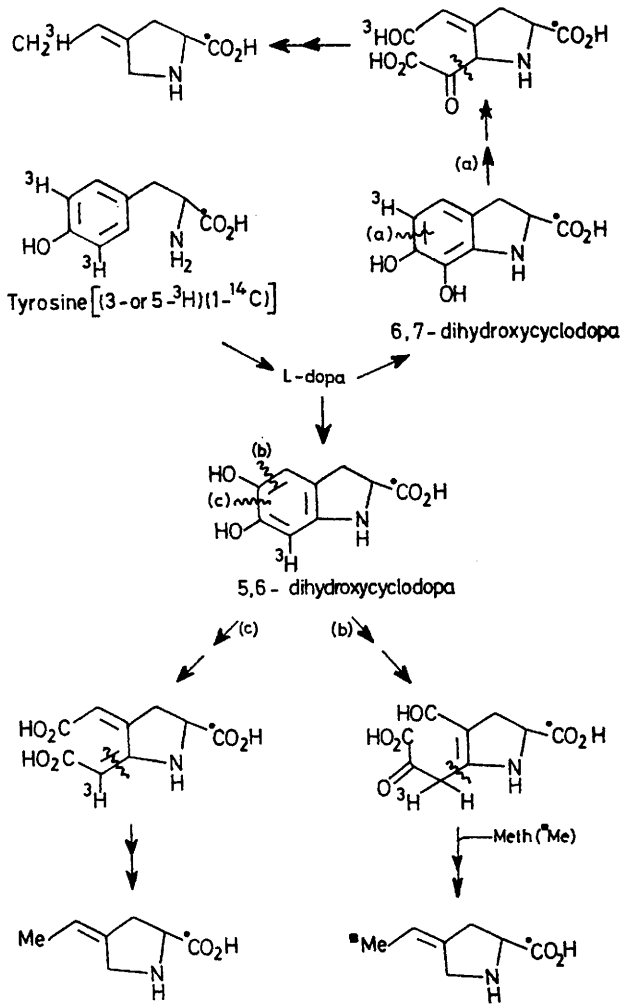
Streptomyces achromogenes was grown in 100 ml shake cultures at 30° in a complex media for 72 h, radioactive precursors were then added and after incubating for a further 12 h the culture was extracted three times with 100 ml portions of ethyl acetate. After drying the ethyl



(II)

acetate over sodium sulphate, the organic layer was reduced to dryness under reduced pressure and the residue dissolved in methanol, cold carrier material added and co-crystallized to constant specific activity. The incorporation data indicate that L-tryptophan (7a-^{14}C) (6·3%), L-methionine (Me-^{14}C) (17·8%), L-tyrosine (*U*-^{14}C) (6·0%) and L-dopa (1-^{14}C) (15·0%) were all efficiently incorporated into DMT.

Based on the known biosynthesis of anthramycin (II) in which it has been shown that the 'acrylamide proline' grouping is derived from tyrosine and methionine[2] the three



SCHEME 2

alternative pathways shown in Scheme 2 for the biosynthesis of the 'ethylidene proline' grouping of DMT can be postulated. It is possible to differentiate between these pathways by a combination of feeding experiments with methionine (^{14}Me-) and doubly labelled tyrosine molecules in conjunction with chemical degradation of the biosynthetically produced tomaymycin molecules.

Upon feeding L-tyrosine [(3- or 5-^{3}H)(1-^{14}C)] (^{3}H : ^{14}C = 7·51) almost exactly one half of the tritium was lost during

its conversion to DMT (^3H:^{14}C = 3·69). In addition, whereas the acetic acid derived from Kuhn-Roth oxidation of the DMT biosynthetically labelled from L-tyrosine (3- or 5-^3H) had virtually the same specific activity as the antibiotic (102%), that from the DMT labelled from L-methionine (^{14}Me-) was almost inactive (2%). These results are only consistent with pathway (a) and rule out the alternatives (b) and (c). This therefore establishes that the ring cleavage of dopa occurs extradiol (*meta*) as is also the case in anthramycin biosynthesis.[3]

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[1] K. Kariyone, H. Yazawa, and M. Kohsaka, *Chem. Pharm. Bull.*, 1971, **19**, 2289; K. Arima, M. Kohsaka, G. Tamura, H. Imanaka, and H. Sakai, *J. Antibiotics*, 1972, **25**, 437.

[2] L. Hurley and M. Zmijewski, *J.C.S. Chem. Comm.*, 1974, 337.

[3] In addition to our evidence in ref. 2 we have also obtained further proof for a *meta*-cleavage pathway using deuterium enriched anthramycin molecules in conjunction with ^1H n.m.r. L. Hurley, M. Zmijewski, and C. J. Chang, submitted for publication.