Simulating a Step in Tetracycline Biosynthesis

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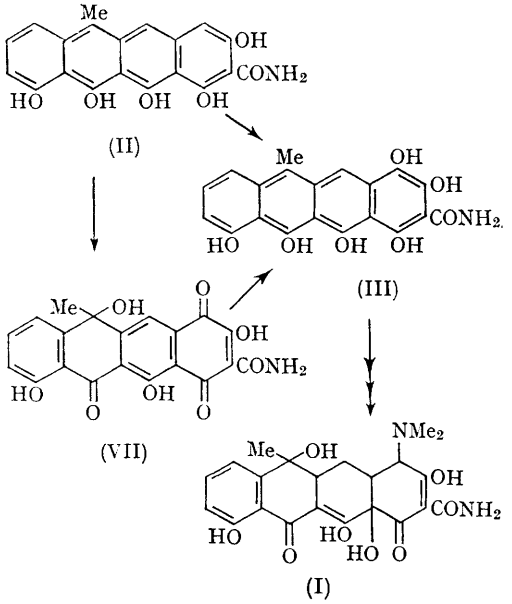
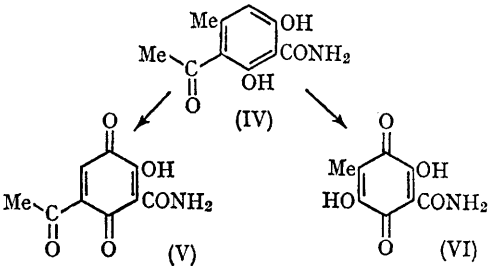
STUDIES by McCormick and his co-workers[1] have established that the biosynthesis of tetracycline (I) proceeds through 6-methylpretetramid (II). The formation of 4-hydroxy-6-methylpretetramid (III) from (II) is an initial step in the process.[2] We have found that this transformation may be achieved readily, *in vitro*.



The action of Fremy's salt, at pH 10, on the carboxamide (IV) which is related in structure to ring A of 6-methylpretetramid, led to the formation of the quinone (V).[3] Moreover, the quinone (VI) was obtained as a major product when the model compound (IV) was treated with oxygen in aqueous alkali;[3] this indicated that hydroxylation of the unsubstituted position in (IV) had occurred under these conditions.



6-Methylpretetramid has been oxidised in a similar way. In the case utilising Fremy's salt there was a complex mixture of products, but oxygenation in alkali led to preferential hydroxylation in the 4- and 6-positions. The product (VII), which was isolated in 25% yield, was identified by comparison with material prepared by degradation of tetracycline.[4] It can be converted, readily, to

4-hydroxy-6-methylpretetramid (III) by a known reaction.[5]

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[3] C. H. Hassall and T. E. Winters, in the press.
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[5] J. R. D. McCormick and E. R. Jensen, *J. Amer. Chem. Soc.*, 1965, **87**, 1794.