

The Conversion of Cyclophenin into Viridicatin

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Summary Evidence is presented relating to the mechanism of acid- and base-catalysed rearrangement of the mould metabolite cyclophenin to its congener viridicatin.

CYCLOPENIN, a metabolite of *Renicillium cyclopium*^{1,2} and *Penicillium viridicatum*,² has been shown by unambiguous, total synthesis to possess stereostructure (I).^{3,4} Early studies on cyclophenin demonstrated its ready conversion into a co-metabolite, viridicatin (II),^{2,5} in both acidic and basic media,¹ and later, an enzyme preparation "cyclophenase" was obtained from *P. viridicatum* which effected the same transformation.⁶ The acid-catalysed and enzymatic reactions produce, concomitant with (II), equivalent amounts of methylamine and carbon dioxide, and, when (–)-[5-¹⁴C]cyclophenin (prepared by *in vivo* incorporation of [¹⁴CO₂H]anthranilic acid)⁷ was subjected to these conditions, label was found exclusively in the evolved carbon dioxide.⁸ A recent article describing results related to the mechanism of the cyclophenin–viridicatin conversion⁸ prompts us to report our own results.

(±)-Cyclophenin (I) was prepared by the sequence outlined below and had spectral properties identical with those of natural material.† Cyclophenin is soluble in basic solution

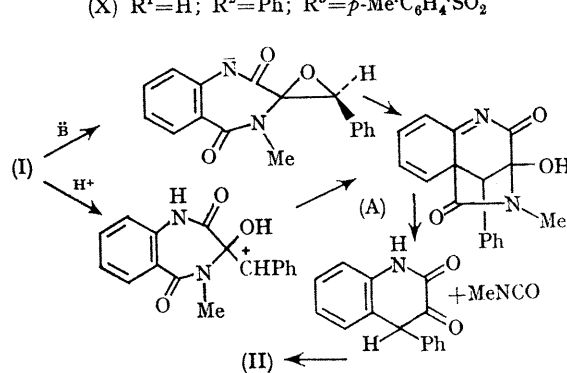
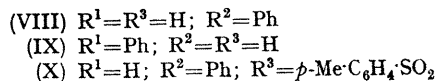
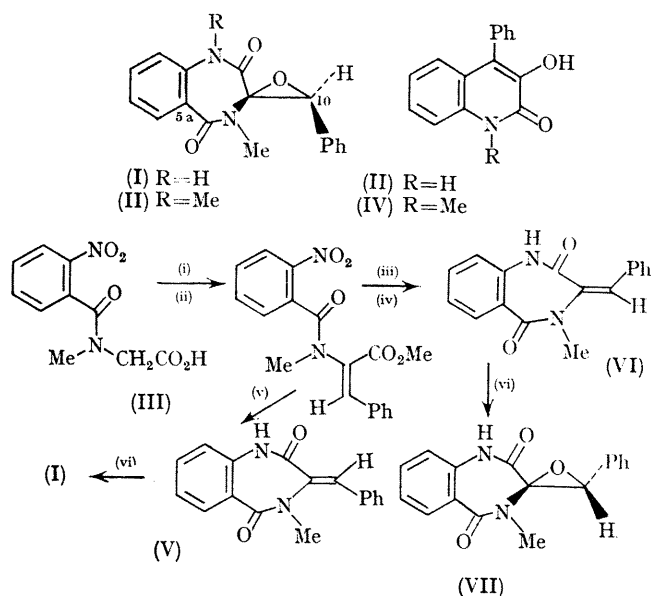
and its ultraviolet spectrum shows a bathochromic shift [λ_{\max} 290 nm. (ϵ 2800) in EtOH to λ_{\max} 312.5 nm. (ϵ 3500) in dilute NaOH], which is reversed upon acidification. Although (I) yields (II) on exposure to either 2N-HCl or 1N-NaOH, (±)-*N*-methylcyclophenin (III), prepared from (I) and diazomethane,² affords *N*-methylviridicatin (IV)⁹ only in the presence of acid. These results imply that removal of the NH-proton of cyclophenin is required to initiate the base-catalysed conversion into (II). It was subsequently found that transformation of (I) to (II) can be effected by warming a solution of (I) in 30% aqueous ammonia and, in this case, virtually the sole product remaining in the lyophilized residue after removal of viridicatin is *N*-methylurea. The nitrogen and two carbon atoms must, therefore, be extruded as a unit (presumably methyl isocyanate) and the methylamine and carbon dioxide detected in the acidic and enzymatic reactions may be the result of a subsequent hydrolytic step. Luckner has also reported isolation of a urea derivative in the Lewis-acid-catalysed rearrangement.⁸

In contrast to (I), which afforded (II), *trans*-3-benzylidene-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,5-dione (V) was recovered unchanged after treatment with sodium

† We thank Professor H. Rapoport for making the comparison of our synthetic (I) with his synthetic and natural materials.

methoxide in refluxing MeOH for 14 hr. Similarly, the *threo*-diol (VIII) and *erythro*-diol (IX), obtained by hydroxylation of (V) and (VI) respectively with osmium tetroxide

A mechanism for the conversion of (I) into (II) which accounts for all the data at hand is presented below. A central feature of this process is bond formation between



Reagents: (i) PhCHO, Ac₂O, 98% H₂SO₄; (ii) MeOH; (iii) H₂-Pd/C; (iv) xylene (reflux); (v) piperidine-MeOH (reflux); (vi) *m*-chloroperbenzoic acid, CHCl₃.

in ether-pyridine, both failed to yield viridicatin in either acidic or basic media. Hence, neither the conversion of (I) nor its unnatural stereoisomer (VII) into (II) proceeds *via hydrolytic* opening of the epoxide function. However, the toluene-*p*-sulphonate (X) of (VIII) affords (II) under all conditions which are effective in the rearrangement of cyclophenin itself, and thus confirms that opening of the epoxide by cleavage of the benzylic carbon-oxygen bond is an integral part of the reorganization process. These results are in agreement with the suggestion that the epoxide oxygen of cyclophenin becomes the 3-hydroxy-group of viridicatin, as inferred from the observation that no label is incorporated into (II) when the rearrangement of (I) is carried out in [¹⁸O]-enriched water.⁸

C-10 and C-5a of (I), a requirement pointed out previously,⁶ and a model of (I) reveals that, in a boat conformation, close approach is possible between these two centres with relatively little steric interference between substituent groups. For this reason, the formation of a tricyclic intermediate (A) would appear to be probable, although attempts to detect this intermediate have so far proved unsuccessful. The scheme proposed here differs in several respects from that suggested by Luckner, Winter, and Reisch,⁸ which fails to account for the base-catalysed rearrangement of (I). The parallels previously noted⁸ between chemical and enzymatic pathways in the transformation of cyclophenin to viridicatin suggest that the active site of cyclophenase may involve both acidic and basic functionalities as well as a geometry which imposes a specific conformation on the substrate.

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